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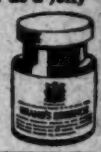

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 12 1950

HUMANISM, HISTORY, AND NATURAL SCIENCE IN MEDICINE*

BY

F. M. R. WALSHE, M.D., D.Sc., F.R.C.P., F.R.S.

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The Linacre Lectureship, to which the Master and Fellows of St. John's College have done me the honour to call me, is, I believe, the oldest medical lecture foundation in this country. It has a tradition all its own in that it was one of the academic activities that survived the greedy spoliations of this University by Henry the Eighth that Latimer was to deplore in 1550, and again because its founder, Thomas Linacre, has a great place in our history, not only as a physician and the translator of the works of Galen from their original tongue but also as the principal restorer of the knowledge of Greek in this country.

In this work of restoration he was one of that small group of English humanists which included Grocyn, Lily, Colet, and Thomas More, who shed such lustre upon English learning in their time; one of whom, Thomas More, was to catch the imagination of all Christendom in his day as the living embodiment of all that was best in Christian Humanism; an ideal by which he lived and, in the manner of his death, endorsed.

What perspectives of opportunity, therefore, this lecture must conjure up in the heart and mind of anyone possessed of imagination and called upon to take his place in the long sequence of Linacre lecturers.

It would be vain for me to hope to rise to the height of this opportunity. I can but do my best to set out in their relevance to medicine three themes which come naturally to the mind in the contemplation of Linacre's life and circle. They are Humanism, History, and Natural Science.

For my shortcomings in a journey that will take me beyond the confines of medicine, as we ordinarily think of it, I ask your charity. And if I venture upon this task, it is not with the hope of completing it, but out of the conviction that to rebuild a bridge between medicine and the humanities is a pressing need; that this building can be done only from the side of medicine; and that someone must make a start if medicine is not to lapse into a mere congeries of techniques, to fail in coherence on its theoretical side, and to suffer the loss of its traditional values. Linacre was a bridge-builder between the ancient world of Hellas and Tudor England. It is not unfitting, therefore, that the Linacre lecturer of to-day should, in however humble a fashion, seek also to be a bridge-builder.

I shall not be derogating from Linacre's just place in history when I submit that perhaps his chief claim to enduring renown amongst us was his reintroduction of Greek to England. He was already an accomplished Greek scholar when, almost by chance as it might seem, he turned aside in his Italian journey to visit Padua, then a foremost centre of medical learning and of philosophy. There with a remarkable celerity he graduated as a doctor of medicine. Upon his return to England the Universities of Cambridge and Oxford hastened to confer upon him the like degree, with an easy liberality that must excite the puzzled envy of the present generation.

I am not enough of a historian to know precisely what could have been the course of the studies so speedily accomplished, but we learn that he defended his thesis with skill and applause against all comers, that within a few years of his return to his native land he had been appointed physician to that formidable patient King Henry the Eighth, and had embarked upon his famous translations of Galen, about which, were I strictly faithful to the provisions of his foundation, I should now be discoursing to you. One of his last acts was to found these lectures, expressing in his Deed of Gift the wish that they should "redound to the glory of God, the true art of medicine, the relief of the fallen, and the increase of the realm." I take leave to say, even in this bleak age of the spirit in which we live, that no nobler ideal of the vocation of the true physician could be proposed.

In a Harveian Oration before the Royal College of Physicians in 1948 I ventured to submit the claim of medicine to a place as of right within the body of the natural sciences. It is not my purpose to-day to reiterate this claim, but rather to propose to you that in its nature and aim medicine transcends the natural sciences; that medicine has in it an element also that properly belongs to the discipline of historical science, and that, ranging high above these, it has, at its best, qualities of humanism that the natural sciences, at least, can scarcely claim. Humanism, History, and Natural Science therefore are, I submit, the elements which medicine, worthily conceived and practised, integrates, or seeks to integrate, into a harmonious whole.

*The Linacre Lecture delivered to the Master and Fellows of St. John's College, Cambridge, on May 6.

Humanism

In his attractive seventeenth-century phraseology Hobbes reminds us that "the Light of Humane minds is Perspicuous Words, but by exact definitions first snuffed, and purged from ambiguity," and there can be few terms in respect of which this process is more necessary than the one now in question—namely, Humanism. Aristotle provided the first apology for an intellectual and secular humanism in his *Ethics*. Boethius, in his *Consolations of Philosophy*, gave us an early and familiar apology for a truly Christian humanism; and since his day, and particularly during the Italian Renaissance from the time of Petrarch onwards, ideals of humanism, secular and Christian, have been many.

In our own time and country Pater and Housman have expounded their views on the subject, and have written of a humanism in which the cultivation of the mind, of an intellectual excellence, is an end in itself.

But it seems to me that the humanism which a Linacre lecturer must put before you must be the Christian ideal and not the purely secular one, though this undeniably has its own intrinsic excellence. With the narrowest of all conceptions of humanism, that which equates it with a classical education, I am certainly not now concerned. Nor do I adopt any of the definitions given in that impressive shorter dictionary which emanates from another seat of learning than this.

Let me say, more positively, to what I do refer by the term "humanism." The Christian world inherited from the ancient world an idea and an ideal of culture which had three aspects: a speculative aspect, the ideal of truth, *veritas*; a moral aspect, the ideal of virtue, *virtus*; and an oratorical and literary aspect, *eloquentia*. And, since we are the agents of thought, speech, and action, this ideal may properly be called humanism.

Here is a humanism that strives for intellectual excellence, on the speculative side for the perfection of the lower reason which is ordered knowledge, *scientia*, and for that of the higher reason which is wisdom, *sapientia*, by which we are enabled to place knowledge in the whole framework of life; while, on the moral side, it includes practical wisdom—that is, prudence. Aristotle in his *Ethics* points out that science deals with things that are of necessity and with universals, while prudence deals with the affairs of men and not with universals only but with particulars. Thus it demands experience.

In the application of science to the practice of medicine the physician needs practical as well as speculative wisdom. He must be governed in his actions by a wise regard for the whole welfare of each patient individually. This regard is the peculiar, the essential, act of the virtue called prudence, which transcends natural science and comes within the category of moral excellence—ethics.

Finally, a complete humanism demands also the literary quality of eloquence: lucidity and conciseness of language and the skilled use of analogy and metaphor, which is what the mediaevals spoke of as rhetoric.

This is the humanism we see so beautifully exemplified in the life of Linacre's youngest and most famous pupil, Sir Thomas More, the patron saint of humanism. To whomsoever may not have read them I recommend the biography of More, and the smaller volume upon More's place in English literature and history, written with such insight by the late Professor R. W. Chambers, himself a rare humanist; works which have done so much to clear away those mists of provincialism and prejudice that have blinded the eyes of so many writers on More.

More's humanism had an eager zest for the things of the mind and a fine sense of proportion—"nothing too much"; a clear sense of the limitations of the State when viewed against the natural rights of the human person, and the courage to resist tyranny in the State; a clear and unfailing vision of what lay beyond finite values; and the grace to look beyond these to the hope of a greater experience in another sphere of existence. Here, then, is the humanism I should like you to associate with your thought of Linacre and of the practice of medicine. It is all implicit in the terms of this lecture foundation, drawn up by him in his last years and already quoted.

This occasion therefore seems to me one singularly appropriate for an exposition of medicine, not primarily as a theoretical and practical activity within the realm of natural science, but as an activity whose full scope and final end transcend natural science. With this confession of faith I turn to my second theme—namely, the relation of medicine to historical science.

Relation of Medicine to Historical Science

Medicine to-day carries the wounds of much ruthless administrative planning, but what she most needs is some intellectual organization from within, and as part of this it is important that we should ourselves undertake some analysis of her relations to the disciplines under which her activities are subsumed.

In a recently published book, *The Concept of Mind*, the Wayneflete Professor of Metaphysical Philosophy in the University of Oxford, Professor Gilbert Ryle, writes that medicine is but "the name of a somewhat arbitrary consortium of more or less loosely connected enquiries and techniques, a consortium that neither has, nor needs, a logically trim statement of programme."

This is surely an erroneous notion of the nature and methods of medicine, lacking both in historical sense and in philosophical comprehension. Yet it is significant that such a definition should find serious utterance, and that in Professor Ryle's mind—if indeed I may apply this term to the neural dispositions of an avowedly anti-intellectualist philosopher—medicine is, as it were, comparable to a travelling country dealer's horse and van, wandering the countryside from farmhouse to cottage, with its odd assortment of wares, chosen in a spirit of opportunism, casually thrown together and having no other relationship than that of contiguity.

Yet, however apt the analogy, the light of common sense shows us that even the travelling dealer has a unity of method and purpose, capable of and needing that trim logical statement of programme that Professor Ryle denies to medicine, either as a possession or as a requirement. Yet it has seemed worth while to cite this pronouncement because it hints at what may, even now, be thought of medicine by many others, even within its own ranks, who have not given serious thought to its history and problems. Who can doubt that the mushroom growth of specialisms, especially therapeutic specialisms, in medicine is tending to its disintegration as a body of ordered knowledge taught by men alert to lift their minds out of the mass of detail? This state of affairs is justification enough for an attempt to subsume medicine under the notions of history and natural science, for now, more than ever, some logical principles must be impressed upon those who will influence thought and practice in the medicine of the future.

In discussing in what sense medicine may be said to come within the discipline of historical science I shall submit,

also, that what is known as psychological medicine belongs primarily to this discipline and not to that of natural science. In doing so, I begin to tread upon dangerous ground, knowing full well that many rhetorical land-mines may be expected to go up noisily and dustily in my track as I proceed upon my hazardous way. Nevertheless, someone must clear the ground if it is to be made fertile soil for the growth of clear and coherent notions in psychological medicine.

Those who are acquainted with Collingwood's stimulating work entitled *The Idea of History,* or with Whitehead's *Modes of Thought,* where the same thesis is briefly expounded, will know something of the argument I shall try to develop, but to many within the ranks of medicine this will be unfamiliar and it is to them primarily that I address my thesis.

History in Medicine

We are prone to take it for granted that our activities in medicine are all to be subsumed under the heading of scientific theory and practice on the one hand, and that of purely empirical and traditional arts on the other. However, in the primary and essential process of eliciting what we call the history of an illness, our activities do not come within any of these categories. We are in fact seeking to collect a record of past events that for us are not sense data, but things that have happened not under our eyes; things that, more often than not, we cannot submit to any process of scientific verification. This record we proceed to subject to a process of critical thought. From its items we select, discard, and assemble in the light of our previous experience; and the final product of our activity is the sublimation of a certain kind of evidence from one source and of a critical study of it from another. Also, since the evidence we thus collect includes not only events that have happened to the patient but, in addition, actions that he has performed, there appears a new element not encountered in natural science—namely, human action. Between a simple event and a human action a distinction has to be made. In short, what we call "the history" in clinical medicine is not a mere chronicle of events, subjected to no analysis or interpretation, but it is a true exercise in historical method, as I shall seek to define this. This is not yet to assert that we are historians in the sense commonly understood by historians, but that we are using their method, which is not the method of natural science.

Distinction Between Natural and Historical Science

Let me briefly elaborate the distinction that I wish to make between natural and historical science, but although I begin from Collingwood's conception of history I shall allow myself the liberty of differing somewhat from him in his application of this conception to psychological factors in medicine.

The prime method of natural science is the observation of events, the flux of which forms a moving spectacle before us, with such verifications and repetitions of this observation as sound factual conclusions may demand. Under the term "observation" I include the method of controlled experiment which Bacon has spoken of as "putting nature to the question." Having observed these events as particulars, we then seek to determine the patterns and sequences into which they fall, and from these to make the generalizations that we speak of as laws of nature. The historian, on the other hand, is not concerned with events which he perceives, nor does he seek to make generalizations, abstractions, or to propound universals. He is concerned with human actions that lie in the past, though they may have their consequences in the present, which have not the quality of sense data as these are understood in natural science. His evidence is the written and archaeological record, to which he applies a critical judgment based on his experience, using those processes of selection and assembly that I have spoken of as of the essence of clinical history taking. To his final conclusion there go the same two elements that we have seen in the clinical history. In both historical science, as the historical expert conceives this, and in taking a clinical history there is a subject–object composition.

Now the historian regards his task as concerned not with simple events as such, but with events as determined by, and expressive of, human thought—that is, with human actions—and his quest is to uncover the motive forces which, for him, are the inside of the event. Events are not spectacles which he observes and seeks to classify, but something that he seeks to go behind so that he may uncover the human thoughts and motives, conscious and unconscious, that they express.

Collingwood gives a simple example that may make this distinction clearer to those who are not familiar with it. He says, "When a scientist asks, 'Why did that piece of litmus paper turn pink?' he means, 'On what occasions do pieces of litmus paper turn pink?' When a historian asks, 'Why did Brutus stab Caesar?' he means, 'What did Brutus think which made him decide to stab Caesar?' The cause of the event for him means the thought in the mind of the person by whose agency the event came about: and this is not something other than the event, it is the inside of the event itself."

It is the function of the natural scientist to ask the first kind of question, but that of the historian to ask the second kind; and, having asked it, he does not proceed to formulate general laws or to indulge in predictions, and in this also he differs from the natural scientist.

The True Historical Method

We come now to consider the relevance of all this to medicine. It is clear that the historian does not regard sequences or patterns of simple events as part of the historical process as he conceives this. Therefore, much of what we elicit and interpret in the taking of a "clinical history" is not history in this general sense, though, I submit, the method we have used is in fact the true historical method.

Yet, as every physician knows from his experience, the elements of "event" and of "human action" do enter into the development and behaviour of bodily illness: there is action and reaction between mind and body, and both contribute to the sum which is presented for elucidation. This is true not only of what I shall continue to call the "history" of the illness, it is true also of the clinical picture presented to our direct observation. I submit, therefore, that even in the apparently and exclusively somatic illness we cannot confine ourselves wholly to the methods of natural science but must take account also of the historical method. Further, owing to the common incompleteness of the data of observation presented to us, we have to read them in the context of the clinical history. Thus the methods of natural and of historical science are closely interwoven in our activities.

Every physician, and especially every teacher of medicine, knows that what is called "history taking" is a task calling for experience and critical thinking, and that it cannot be learned with the ease to which the techniques of clinical examination often lend themselves. This is in

accord with what, following Collingwood, we have said of the nature of historical evidence, and of its criticism, selection, and assembly in the writing of history : a complex intellectual exercise in which the evidence is given life and meaning by the historian's own contribution of thought and knowledge. Therefore, we need not be surprised that the young student so often gives us those flat and incoherent chronicles, thickly sown with irrelevances, that are too frequently allowed to pass muster as medical histories.

History and Psychology

It is when we come to consider psychological medicine, and what we may term psychologically determined illness, that the analogy between medicine and history leaps to the eye. Here, I submit, we are truly within the realm of historical science as the historian strictly defines it. Psychology, or the science of human nature, as our eighteenth-century philosophers were wont to call it, has since their time sought assiduously to establish itself as a discipline within the field of the natural sciences, and has claimed to use their methods.

In the case of psychological medicine, or psychopathology, this claim has been eloquently stated by Bernard Hart in his Goulstonian Lectures of 1926. He regards the data of the psychologist in medicine as strictly comparable in character to those of natural science, and goes on to say that a scientific concept "must explain the observed facts, and must be capable of verification by repeated reference to experience and experiment." These postulates he clearly believes to be fulfilled in psychological medicine. Yet surely the aim of psychological medicine is the discerning and unravelling of the mental processes, conscious and unconscious, that lie behind the "observed facts," which are in their origin and nature merely derivative phenomena and of infinite variability and unpredictability. The essential data in psychology, as we find it in medicine, are the mental processes behind the façade of the so-called "observed facts." It is surely a *non sequitur* to invoke the canons of natural science in this situation. The postulates propounded by Hart are not, and cannot be, fulfilled by psychological medicine, and it is meaningless to speak of "verification by repeated reference to experience and experiment" in this connexion. Elsewhere in the lecture he says that "the introduction of purpose removes psychology from the mechanistic sciences, but this does not justify its removal from the whole field of science." Here Hart seems almost trembling on the brink of awareness that psychology does not belong to natural science. However, he goes on to place it with biology. Yet the word "purpose" is not unequivocal, for teleology in biology is not the "purpose" that determines human actions. Such are the pitfalls of linguistics.

It is of course virtually impossible to generalize about psychology as we find it in medicine to-day, because it has no unity of method or of concept, and it continues to be regarded by its exponents as "scientific" in so loose and undefined a way that the adjective has no clear connotation. Nevertheless, countless expositions make it certain that it is natural science which the psychologist has in mind when he uses the term.

Of its possible relation to historical science we find no word in the superabundant writings on psychological medicine. Even that most lucid and philosophic critic of Freudian method, psychology, and philosophy, Maritain, in his attempt to assess and orient them, shows no realization of the possibility that much of the difficulty in determining their status would be resolved if they were measured against the standards and methods of history and not against those of natural science.

Yet how far removed from the methods of natural science are the Freudian psychology and philosophy Maritain indicates in the following verdict : "It is in the techniques of interpretation (that is, of dreams and free association), and especially in the use of symbolism, that Freud and his disciples have been led to the profusion of the arbitrary, of obsessional dogmatism, and of pedantry."

Even in the latest review of the development of psychological medicine by Rickman it is stated that the unravelling of the meaning of dreams is "the main tool of research," and the concepts derived from the use of this tool are spoken of as within the realm of "scientific thought," though what order of science we are not told.

An Illusion

For any who may still cherish the illusion that Freudian psychology has any discoverable relation to natural science in its methods or concepts, a careful reading of Rickman's article, "The Development of Psychological Medicine," should prove an effective remedy.

The fact surely is that the psychologist in medicine is not primarily concerned with events, nor does he use the sense data that are the material of natural science, but his first concern is the application, more or less imperfect, of the historical method to the fragmentary and fugitive records of human thinking and action which he can glimpse in his patient's mental past. It is upon this application that all depends.

The springs of human action which are his quest are not data of observation amenable to experimental control or classification. If they are to be revealed at all it is only by the method of historical thinking in which the inquirer collects his record of evidence, subjects it to critical assessment and selective assembly, and then formulates conclusions that have the duality of origin I have already proposed for the ordinary clinical history.

In this process he aims to understand the mental activities underlying the concrete situation he is studying, and he can do this effectually only by rethinking or reliving these activities in his mind and in the context of his own knowledge. The medical psychologist's problem is a concrete historical one and does not and cannot lead to the formulations of universals, for there is no blue print, no master key, to the springs of human thoughts and actions, applicable to all persons at all times and in all circumstances, and no natural laws for the human mind as natural laws are generally conceived.

We may therefore conclude that the steady endeavour of two centuries to fit psychology within the realm of the natural sciences is based upon a false analogy, to which the very term "human nature" lends colour. This analogy has gravely retarded the growth of a true science of psychology under the aegis of history.

In medicine the easy illusion that they are natural scientists, using the methods of natural science, has not saved medical psychologists from wandering within a labyrinth of conflicting speculations and methods, blown about by every wind of doctrine ; from exotic symbolist systems on the one hand to extremes of anti-intellectualism on the other, and through the latter to a new psychiatry which in effect dementalizes mind and seeks to account for its activities in terms of "nerve nets," "reverberating circuits," and "feedback mechanisms" in the cerebral cortex—that is, to provide physiological accounts of mental activities and in so doing to leave no room for psychology.

Wanderings of Psychological Medicine

This constant wavering of psychological theory in medicine between allegory and machinery, and of psychological practice between the exegesis of dreams and what in a barbarous neologism is called "psycho-surgery," does not allow a resting-place for the psychology of the modern psychiatrist within the confines of any known scientific discipline. It has become a chaos of conflicting allegorical systems, of pseudomysticism, and of "hit or miss" mutilations of the brain that have no ascertained scientific basis.

Surely, in such a situation, the claim to come within the realm of natural science is revealed as no more than the overt expression of unconscious yearnings to acquire some sort of academic prestige within the world of ordered knowledge. These wanderings of psychological medicine in the wilderness, not yet ended, always recall to my mind the title of one of Captain Marryat's stories for boys, *Japhet in Search of a Father*.

Yet, despite this profoundly unsatisfactory situation, there are of course sage medical psychologists who do use the historical method in its strictness, though they may not know it for such. When these men do turn to physical methods of treatment they remain fully aware that these have no scientific basis, but are wholly empirical procedures acting in unknown fashion but having the possibilities of pragmatic justification in particular instances. Nevertheless, it is surely clear that the hope of an advance towards coherence and scientific status for psychological medicine would be immeasurably increased if its exponents thought out the nature of their subject and became aware of the scientific discipline to which it should be affiliated—that of historical science.

If there be a body of psychological knowledge within the bounds of natural science it is that physiological psychology which has sense data to observe and classify in the forms of nervous and muscular activity which are the physical expression of current mental causes. Of such a physiological psychology there is a distinguished school in this university, but its aims, methods, and results in no way resemble those of the so-called medical psychology which shares with it little but the substantive common to their names.

It would be over-sanguine to look for a ready assent from the psychologist in medicine to a proposition so contrary to all he has hitherto believed regarding the nature of his activities and their place in the body of science. Yet it may be that the moment will arrive in which he is found willing to turn to some epistemological contemplation of his special body of knowledge and theory. The need is surely urgent, for there is a place for a scientific psychology in medicine under the aegis of historical science, a discipline as worthy of our esteem as that of natural science. To seek to remove psychological medicine from the one domain to the other is not to derogate from its status and importance.

Yet the historical method has its own ideals of truth; and the realization of these is not compatible with intellectual submission to fixed symbolic systems in the interpretation of human action. Such lesser loyalties have no place in any scientific discipline, and with their advent there creep in, as attendant evils, myth and pseudomysticism, an obsessional dogmatism, and a sacerdotalism of outlook that have always been the greatest enemies of science.

The medical psychologist must be elective if he is to preserve his intellectual freedom and integrity, and in the interpretation of human records which are the essential data of his study his own knowledge and critical insight must be the dominant instruments.

A Dissent

Before I leave this subject I venture to make one dissent from Collingwood's view of the proper task of psychology. He says: "In realizing its own rationality mind also realizes the presence in itself of elements that are not rational. . . . These irrational elements are the subject matter of psychology. They are the blind forces and activities in us that are part of human life as it consciously experiences itself, but are not parts of the historical process: sensation as distinct from thought, feelings as distinct from conceptions, appetite as distinct from will. Their importance to us consists in the fact that they form the proximate environment in which our reason lives, as our physiological organism is the proximate environment in which they live. They are the basis of our rational life, though no part of it. Our reason discovers them, but in studying them it is not studying itself."

Yet surely reason does not work in an emotional vacuum, and in studying human actions it is impossible to separate, save by the process of abstraction, the emotional from the rational elements in our actions and their motive forces. And if history is the study of the concrete, this abstraction cannot be made save for purposes of discourse and logical analysis. I venture to submit, therefore, that we cannot regard psychology as concerned solely with the irrational in us, or allow that the latter is not involved in the historical process which it is the psychologist's business to study.

Conclusion

I believe, then, that history and natural science are recurrent themes, closely interwoven in medicine, not always recognized by us as such as we pursue our activities, but always present. I believe, too, that we shall think more clearly if we know that this is so.

At least those of us who teach medicine, and bear responsibility for the future of medicine, should have some awareness of the nature of our subject. In his book, *The Idea of the Universe*, Collingwood, whom I have quoted so often, observes that "a man who has never reflected upon the principles of his work has not achieved a grown-up man's attitude towards it; a scientist who has never philosophized about his science can never be more than a second-hand, imitative journeyman scientist. A man who has never enjoyed a certain type of experience cannot reflect upon it."

These thoughts must be my justification for the excursion I have made this afternoon upon territory which the physician will enter with diffidence and tread with circumspection, yet the physician is the man best placed to reflect upon his experience and to philosophize upon it.

This foundation of Linacre's has seemed to me an admirable opportunity for such reflection, and I venture to think that he might not altogether disapprove the intention which informs my lecture, though he might well have thought less highly of its realization.

In conclusion, although the occasion that calls us together is not the only Foundation we owe to Linacre's concern for the advancement of medicine, it is the only one which has been consistently devoted to humanist and academic themes and ends.

To use the brief recurrent occasions which this lecture affords us amidst the press of material preoccupations in order to dwell upon these values and purposes is not mere escapism. It should be refreshment.

Doubtless the cynic will think and say otherwise, but cynicism is too often only the threadbare cloak for timidity in the face of threats to our traditional values. The idealist, as he looks at the world around him, which he has so little

share in moulding, need not feel ashamed if he continues to cherish and to advocate his ideals.

Only such an ideal of humanism as I have sketched, with its emphasis upon practical wisdom, and such reflections upon the nature of our activities as I have so imperfectly put before you, can save the loss of our traditional values and keep us aware of the nature of what we are thinking and doing. Yet, whatever be true of the latter, there can be no doubting that the practice of medicine flourishes most when doctors think most highly of their functions; when they remember that prudence governs the employment of science, and that in the last resort they are concerned with the ultimate particular thing, the human person, whom science by itself is inadequate to comprehend.

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(Of the works quoted hereunder I owe a special debt to the Aquinas Papers of the Revs. Kenelm Foster, O.P., and D. J. B. Hawkins)

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INSULIN-INDUCED SKELETAL ABNORMALITIES IN DEVELOPING CHICKENS*

BY

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According to C. S. Stockard (1912) developmental anomalies of various types and degrees cause "the death of about 23% of the human race before or shortly after the time of birth and handicap(s) a certain proportion of the survivors throughout their lives." During the last few decades the discovery of genetic factors leading to malformations has attracted a great deal of attention, while research in the field of environmental teratogenic factors has lagged behind.

There exists a widespread belief among laymen as well as among physicians that single and multiple congenital malformations are always the result of changes in the germplasm—in other words, they are genetically determined and hereditary. I do not, for a moment, minimize the role of genetic factors in the causation of congenital anomalies, but it has been shown in recent years that developmental processes can be altered by environmental disturbances as well as by abnormal genes. It will be of great interest to the geneticist to know that types of congenital malformations which are sometimes genetically determined, such as microphthalmos, cleft palate, and certain skeletal abnormalities, can be produced in the offspring not only by maternal nutritional deficiencies and by roentgen irradiation, but also, at least in some animals, by the deliberate introduction of certain substances during embryonic growth.

New momentum to this line of thought has been given by the valuable epidemiological observations first made by Gregg in Australia in 1941. Since then evidence has accumulated that the contraction of rubella by the mother early in pregnancy is related to the development of congenital anomalies like cataract, heart disease, and deafmutism in the offspring. This has naturally raised the question whether other infectious diseases, particularly those due to a virus, such as mumps, measles, and chickenpox, may cause similar defects. It may easily be that the more severe infectious diseases contracted during pregnancy are prone to result in abortion or miscarriage, whereas comparatively milder ones like rubella can give rise to congenital anomalies in the foetus without jeopardizing its life.

In 1943, while investigating the role of glycogen granules in hypertrophic cartilage cells during endochondral ossification, I made an accidental observation as a result of which I became interested in the insulin-induced skeletal abnormalities in developing chick embryos. In the course of a series of experiments I introduced 5 units of insulin into hens' eggs at various intervals after the beginning of incubation and noticed that some of the chicks showed *x*-ray appearances resembling osteogenesis imperfecta in the human, that some had developed abnormalities of the spinal column like spina bifida, with partial or complete suppression of development of some vertebrae, while others showed deformities in the limbs. I have observed that "synthalin," too, can induce certain skeletal deformities when injected in the same way, and an account of these deformities will be given in a separate paper. Unfortunately my investigations were interrupted during the war, and for one reason or another I could not renew my experimental work until I came to Liverpool in October, 1947.

Material and Method

My experiments have been conducted mostly with eggs from brown leghorn matings. I have used a simple apparatus not only for testing the fertility of an egg before injection but also for transilluminating it while drilling a hole into the shell and injecting into the yolk. In this way I have avoided injuring the embryo and the chorionic blood vessels. A fine dental drill held in a small chuck has been used to make a hole in the egg-shell, which has been sterilized with spirit. A tuberculin syringe fitted with the finest hypodermic needle ¼ in. (1.9 cm.) long has been found most suitable for making the injections. This length of needle enables one to inject into the yolk.

In my experiments I have used crystalline insulin dissolved in distilled water and made up to a strength of 40 units in each millilitre. The doses given varied from 0.05 to 6 units at different intervals after the beginning of incubation. Calculated on the basis of the human dose, 6 units to a developing chick embryo may appear to be distinctly excessive. But Riddle (1923) and others have shown that birds are highly resistant to insulin and can therefore survive a dose of insulin 30 times as strong as that which would kill a rabbit. Whenever the volume of the solution injected has exceeded 0.05 ml. an additional hole has been drilled into the egg-shell in the region of the

*Based on a paper read at the Liverpool Medical Institution on January 19, 1950.

air sac in order to prevent undue increase of pressure inside the egg. I should perhaps make it perfectly clear, at this stage, that only one injection of insulin is given into the egg, and no more either during the remaining period of incubation or after hatching.

After making the injection the needle is carefully removed without injuring the embryo or the chorionic blood vessels, and the holes are sealed and the egg returned to the incubator. By the same technique control eggs have been injected with the same quantities of physiological saline and incubated in the same incubator. Embryos have been removed at varying intervals before hatching for histological and other investigations. All chicks which survived 14 days after the beginning of incubation and those that hatched out alive either by themselves or with help, as in the case of deformed ones, have been *x*-rayed. All the live chickens, insulin-treated as well as the controls, have been fed on a nutritious diet rich in vitamins and reared under conditions equal in every way. It should be noted here that nearly all the insulin-treated chickens are smaller and more delicate than the controls, so that they have to be reared with special care.

Observations

I do not propose to enter here into a detailed discussion on the histological, biochemical, and other aspects of the problem, which will be dealt with later, but rather to give a preliminary survey of the more important observations that have so far been made.

Insulin-Induced Skeletal Abnormalities

Day of Injection after Starting of Incubation	Part of Body *Primarily* Affected by Insulin
0–2nd day	Vertebral column
3rd day	Claws
4th and 5th days	Limbs; beak
6th day	Hip (congenital dislocation of hip)
3rd to 6th days (high doses of insulin)	Generalized developmental disturbance of bone resembling osteogenesis imperfecta

Broadly speaking, insulin seems to affect primarily the part or organ which is in the most active stage of development or differentiation at the time of injection, though the growth of the embryo as a whole is retarded to a degree varying with the dose of insulin. The accompanying Table and Fig. 1 give some idea of the type of deformity that has been induced by insulin in relation to the time of injection after the starting of incubation of the egg. If it is remembered that during the development of the limb bud it is the distal part that first shoots out, as it were, from the side of the trunk, then it is easy

FIG. 2.—Spina bifida in an embryo treated with insulin 24 hours after incubation and removed from the shell alive on the 20th day of incubation.

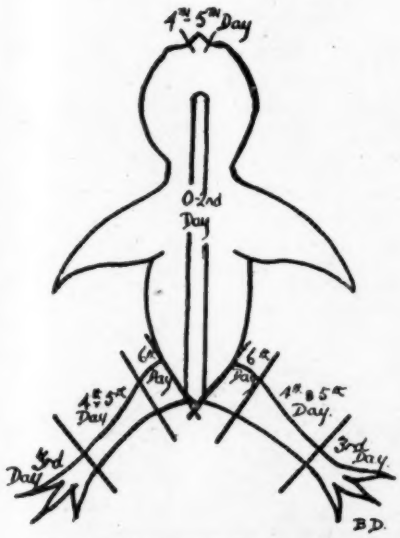

FIG. 1.—Diagram illustrating the type of deformity induced by insulin in relation to the time of injection into the egg after incubation.

FIG. 3.—Divarication of claws. Note the arched upper beak ("parrot beak"). (20-day-old embryo treated with insulin on the third day of incubation.)

FIG. 4.—Adduction deformity of the claws resembling clubfoot in a 20-day-old embryo treated with insulin on the third day of incubation.

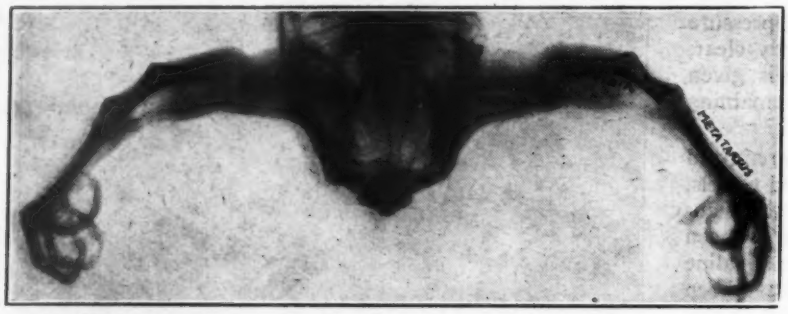

FIG. 5.—Radiograph of a 3-weeks-old chicken with bilateral dislocation of the knee. Note the pathological fractures of both tibiae and the marked buttressing of the concavities of the bowed bones by subperiosteal new bone. (Injection of insulin into the egg on the fourth day.)

to understand the significance of Fig. 1. Within the range of 0.05 to 6 units of insulin that I have injected, both the incidence and the severity of the deformities seem to increase with the dose of the hormone. Figs. 2–11 illustrate the various abnormalities, with appropriate controls for comparison. A generalized developmental disturbance of bone resembling osteogenesis imperfecta has been induced by injecting high doses of insulin between the third and the sixth day of incubation.

FIG. 6.—Deformity of the limbs as seen in arthrogryposis in a 20-day-old embryo treated with insulin on the fifth day. Note the "parrot beak."

Ossification in the Chick

As the process of ossification in the long bones of birds differs in certain essential respects from that of mammals, it is necessary to outline briefly the normal process of ossification in the chick before considering the abnormalities in ossification induced by insulin. Ossification of a long bone in the chick comprises the following four stages :

1. *Formation of Perichondral (Periosteal) Bone.*—The perichondrium deposits a layer of bone on the surface of the cartilage near its centre, thus forming a bony ring, which gradually lengthens into a hollow cylinder by extending towards the ends of the cartilage. This is illustrated in Fig. 12. The perichondral bone is naturally thickest in the centre of the shaft and tapers towards the extremity of the cartilages.

2. *Absorption of Cartilage.*—The matrix softens in the centre of the shaft, and the cartilage is replaced by the fundamental tissue of the marrow. This process extends towards the ends and is faster in the region of the cartilage subjacent to the perichondral bone than in the centre. In this way there remain two terminal cone-shaped cartilages, and the ends of the cones project into the marrow cavity.

3. *Calcification of Cartilage.*—Salts of lime are deposited in the matrix of the cartilage at the ends of the marrow cavity.

4. *Endochondral Ossification.*—Osteoblasts within the marrow cavity deposit bone on the inner surface of the perichondral bone.

It is worthy of note that in birds there is no independent epiphysial centre of ossification in the long bones such as exists in mammals. The ends of the bones remain cartilaginous and provide for growth in length. Growth in diameter of the bones takes place from the periosteum, and is accompanied by enlargement of the marrow cavity owing to simultaneous absorption of bone from within. It is thus obvious that in time all the endochondral bone is removed from the shaft, though some may remain in the spongy ends.

Effect of Insulin on Ossification

We may now see how insulin interferes with the normal process of ossification by comparing the photographs of

FIG. 7.—Generalized developmental disturbance of bone resembling the "prenatal type" of osteogenesis imperfecta with marked stunting in growth (compare with Fig. 8 on the same scale). Note the deformities of the limbs and beak. (20-day-old embryo treated with a high dose (5 units) of insulin on the fifth day of incubation.)

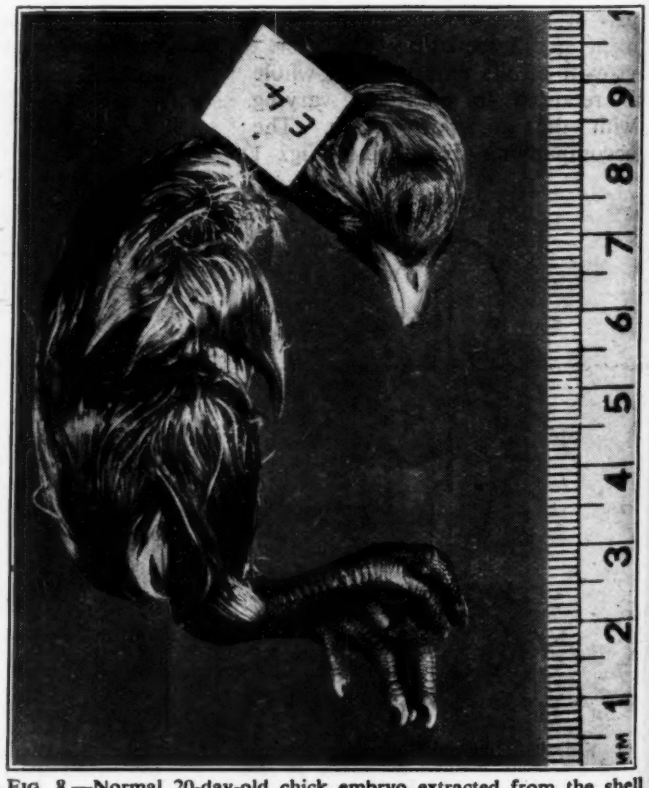

FIG. 8.—Normal 20-day-old chick embryo extracted from the shell before hatching.

FIG. 9.—Radiograph of the skeleton of the same embryo as in Fig. 7 (× 2). Note the deformities of the various bones due to pathological fracture and bending (mollities). Observe the defective ossification and also lack of development of several vertebrae in the distal part of the vertebral column.

FIG. 10.—Radiograph of a 20-day-old normal embryo for comparison with Fig. 9.

enlarged mid-sagittal sections of the tibiae taken from insulin-treated and normal chick embryos of corresponding ages. The possible mechanism of action of insulin is discussed below.

Fig. 13 shows a mid-sagittal section of the tibia from a 20-day-old insulin-treated embryo, and Fig. 12 represents a mid-sagittal section of the proximal half of the tibia from a 20-day-old control embryo for comparison. The special features to be noted in the case of the insulin-treated one are the deformity, the pathological fracture, the stunted growth, and the lack of subperichondral ossification as compared with the corresponding control. Fig. 7 is a photograph of a 20-day-old excessively stunted chick embryo showing evidence of a generalized developmental disturbance of bone resembling osteogenesis imperfecta (" prenatal type "), while Fig. 9 is a radiograph of the same embryo showing the various deformed bones and pathological fractures.

FIG. 11.—Radiograph of pathological fracture of the left tibia in a 5-months-old cockerel with insulin-induced osteogenesis imperfecta (resembling " post-natal type ").

The occurrence of a pathological fracture at the distal third of the tibia has been noted with great regularity in such chicks. It may be recalled that this is the favourite site for pseudarthrosis in children. Fig. 11 shows the radiograph of a pathological fracture of the left tibia in a 5-months-old cockerel with insulin-induced osteogenesis imperfecta (" post-natal type ").

Deformities of the Beak and other Malformations

A highly arched upper beak was often associated with the limb deformities, and, much less commonly, a short upper beak and crossing of the beaks were observed. Apart from the skeletal abnormalities, I have noticed only

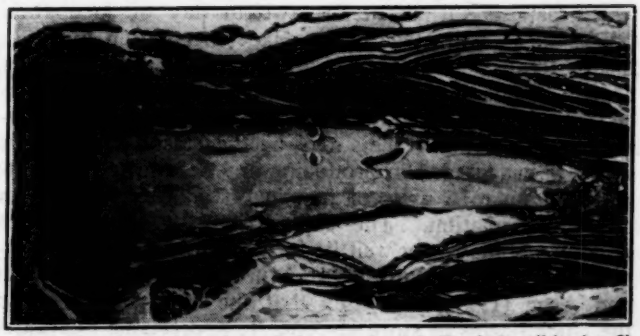

FIG. 12.—Sagittal section of the proximal half of the tibia (× 8) of a normal 20-day-old embryo stained with haematoxylin and eosin. Note that the subperichondral bone is thickest in the centre and tapers towards the extremities. (The perichondrium, together with the subperichondral bone, was partially detached from the proximal cone-shaped cartilage of the tibia during preparation of the section.)

FIG. 13.—Sagittal section of the whole of the tibia (× 7.5) from a 20-day-old insulin-treated embryo. The pathological fracture, the deformity of the tibia, the thickening of the periosteum, and the defective subperiosteal ossification all suggest the condition of osteogenesis imperfecta.

certain anomalies of the eyes such as anophthalmos, microphthalmos, and buphthalmos, the last-named almost always accompanied by blindness. It is interesting to note that all the malformations that have been induced by insulin in my experiments so far have been confined to the skeleton and the eyes. The reasons for this selective action of insulin are given below.

Discussion

The question naturally arises whether these deformities are due to the trauma caused by the injection or to any specific action of insulin. Saline in quantities very much larger than the volumes of insulin solution has been injected into hundreds of control eggs and no deformities have resulted; and injections of parathormone (up to 5 units), calciferol (up to 2,000 i.u.), and radioactive phosphorus (up to 20 microcuries) have been made, also without any resulting deformities. Insulin inactivated by the methyl-alcohol-hydrochloric method of Charles and Scott (1931) has been injected and no deformities have appeared, whereas, when inactivated insulin was reactivated by alkali and then injected the deformities have occurred. I am satisfied, therefore, that the possible trauma of injection is not a factor in causing the abnormalities and that insulin has, in fact, a very specific effect.

There are further reasons for holding this view on the specificity of insulin. Insulin, if injected during the first week of incubation, produces a definite hypoglycaemia which persists till about the twelfth day of incubation (blood sugar estimated by the Hagedorn–Jensen method). Insulin-treated embryos which survive seem to recover normal blood-sugar levels from their own resources between the twelfth and the fourteenth day after the beginning of incubation. This may be the reason why I have so far not succeeded in producing any deformity by injecting even up to 6 units of insulin on or after the twelfth day of incubation. The explanation for this apparent discrepancy may very well lie in the experimental observations made by Idzumi (1924), Murray (1926), and Potvin and Aron (1927), indicating that the embryonic liver in the chick begins to store glycogen in appreciable quantities on or about the eleventh day of incubation, and it is only thereafter that the carbohydrate metabolism is controlled by interaction of the various hormones concerned. Presumably this unchecked insulin hypoglycaemia until about the twelfth day of incubation could result in damage to embryonic cells which, according to Needham (1926), almost exclusively metabolize glucose during the early developmental stage of the embryo. It is generally recognized that insulin enables the tissues to utilize glucose, but, if the

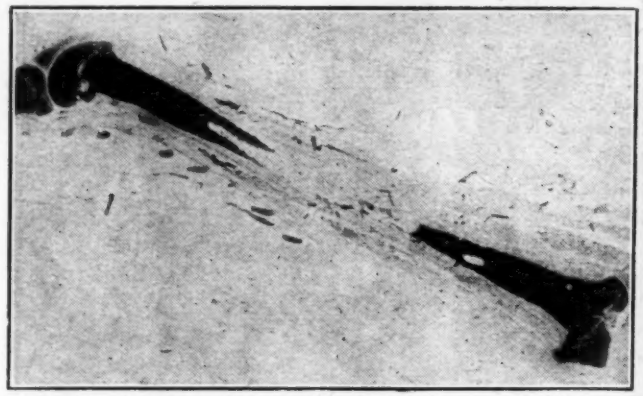

FIG. 14.—Sagittal section of tibia (× 7) of a normal 12-day-old embryo stained with toluidine blue. The cartilaginous core of the tibia has been stained deeply by this selective stain, whereas all the rest of the tissues in the section, including subperichondral bone, appear faintly tinted. The unstained area between the cones of cartilage in the middle of the bone represents the newly forming marrow cavity.

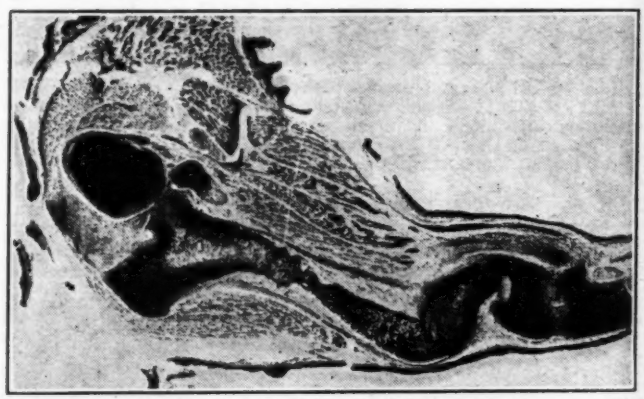

FIG. 15.—Sagittal section of tibia (× 15) of an insulin-treated 12-day-old embryo stained with toluidine blue. Note the marked stunting and deformity of the tibia as compared with the normal in Fig. 14. There is no marrow cavity, the whole sagittal section being filled with cartilage, which has, however, been stained much less intensely by the specific stain owing to poor chondroitin-sulphuric acid content in cartilage cells, many of which show degenerative changes as seen in Figs. 18 and 19.

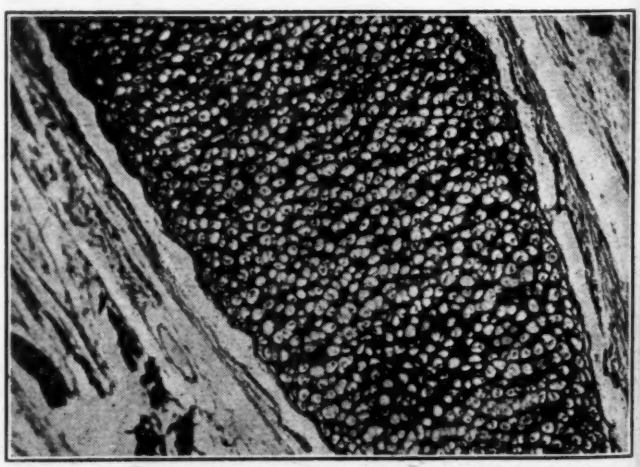

FIG. 16.—Photomicrograph (× 60) of the cartilaginous core from the tibia of a normal 10-day-old embryo stained with toluidine blue. Cartilage cells are stained deeply by this special stain and appear normal.

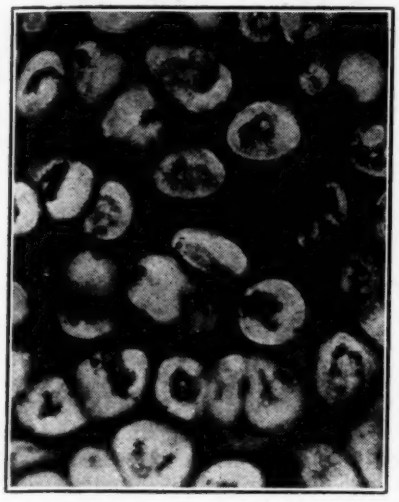

FIG. 17.—Same as Fig. 16 (× 450).

FIG. 18.—Photomicrograph (× 60) of the cartilaginous core from the tibia of an insulin-treated 10-day-old embryo stained with toluidine blue. Note the moth-eaten appearance of the cartilaginous core and the debris of disintegrating nuclei of degenerated cells.

FIG. 19.—Same as Fig. 18 (× 450).

blood sugar is persistently low and glycogen is not stored in the liver during the early stages of development, then it is easy to understand how cellular metabolism will continue to be abnormal as long as the hypoglycaemia lasts.

Needham (1926) has also observed that in the early stages of development in the chick there is a larger proportion of glucose not accounted for by glycogen or free glucose than at any other time. According to him this combined glucose is probably a "mucoprotein glucose," and its importance in the early stages may be correlated with the primitive gelatinous intercellular matrix in which embryonic cells at that time grow and migrate. It is known that cartilage and parts of the eye such as the cornea, vitreous humour, and the sclera, which has a special inner layer of hyaline cartilage in birds, are all rich in substances of the mucoprotein (glycoprotein) type, and it is significant that the insulin-induced abnormalities that I have observed so far have been confined to the skeleton and the eyes.

With a view to the investigation of the effect of insulin treatment on the mucoprotein content of developing cartilage I have employed Lison's histochemical technique for localizing the chondromucoid, which contains chondroitin sulphuric acid, by staining with a basic metachromatic aniline dye such as toluidine blue. Lison (1935) has presented evidence that the metachromatic reaction is specific for chondroitin-sulphuric acid, the affinity of which for the dye is so great that even in very high dilutions (approximately 1 in 250,000) the chondromucoid is stained deeply while the other tissues are faintly tinted by the dye. The contrast between the arresting red-violet of the chondroitin-sulphuric acid and the faint blue colour of the surrounding tissues facilitates a comparative analysis of the distribution and the amount of the chondroitin-sulphuric acid in the cartilaginous skeletons of the insulin-treated and control chick embryos of corresponding ages.

By employing this technique I have observed that there is not only very marked stunting of the cartilaginous skeleton in the insulin-treated chick embryos as compared with the controls, but also the cartilage cells in the former show varying degrees of degeneration and exhibit less affinity for the dye owing to a low chondroitin-sulphuric acid content (Figs. 14–19). It is suggested that such degenerative changes in the cartilaginous skeleton may be followed by deformities, defective ossification, and pathological fractures which may be caused by the vigorous embryonic movements that can be observed from an early period of development, and thus may eventually result in a condition resembling osteogenesis imperfecta.

As mentioned at the beginning of this paper, several nutritional deficiencies have been shown to give rise to congenital malformations. Ivanovsky (1923), in a report on the physical modifications of the population of Russia under famine, remarks: "The number of children either prematurely born or stillborn, monsters, and children with different anomalies considerably increased during the famine." In India and Japan stillbirths, premature deliveries, and congenital malformations have often been reported to be the result of maternal vitamin-B deficiency. Byerly and his co-workers (1935) obtained short-legged embryos from eggs of chickens on a deficiency diet whose effects were reversed by wheat-germ, liver, and whey. Romanoff and Bauernfeind (1942) demonstrated that riboflavin deficiency gave rise to short-legged embryos. Couch and his co-workers (1948) obtained similar abnormalities with eggs from biotin-deficient hens.

It was reported by Warkany and Nelson (1940) that female rats reared and bred on a diet deficient in riboflavin gave birth to offspring a third of which had congenital skeletal abnormalities. The malformations consisted of shortening of the mandible, tibia, fibula, radius, and ulna. Histological examinations revealed that not only osseous but also cartilaginous and pre-cartilaginous structures were deformed in a manner similar to the insulin-induced deformities. It is interesting to note that the tibiae were affected in a high proportion of the deformed offspring as in the case of insulin-induced skeletal deformities. When riboflavin was added to the maternal diet no abnormal young rats were obtained. This new knowledge in the field of nutrition deserves special attention, since it demonstrates the effect of vitamin deficiencies upon the earliest processes of growth and differentiation.

It is well known that the yellow enzyme (containing riboflavin), coenzyme I, and coenzyme II (containing nicotinamide) participate in the breakdown of carbohydrates in the tissues. Spratt (1949) has presented experimental evidence for the existence of the typical phosphorylating system in the early chick embryo. One can therefore anticipate that deficiency of phosphorylating enzymes, produced by lack of vitamin-B complex, may induce malformations in the same way as insulin hypoglycaemia can,

by causing disturbances to cellular carbohydrate metabolism at critical periods during development. Further, I have experimental proof that insulin-induced deformities can be prevented to a remarkable extent by injecting nicotinamide and riboflavin into eggs along with insulin, and details of this work will be given in another paper dealing with the preventive aspect of the problem.

Summary

Though genetic factors play an important part in the causation of congenital anomalies, it has been shown in recent years that certain environmental factors can interfere with the normal developmental processes in the embryo.

An account of the skeletal abnormalities induced by insulin has been given.

It has been suggested that unchecked insulin hypoglycaemia during the early stages of development may adversely affect the development of the cartilaginous skeleton and of the eyes by depriving them of their essential constituent mucoprotein to varying degrees.

This experimental research has been conducted in the Department of Orthopaedic Surgery, University of Liverpool, with the aid of a scholarship granted by the Government of India till October, 1949, and thereafter with a Fellowship awarded by the University of Liverpool, and my grateful acknowledgments are extended to them. I wish to thank Mr. Bryan McFarland, director of orthopaedic studies, and his assistant, Mr. G. V. Osborne, for providing the facilities for carrying out this research; Sir Edward and Lady Mellanby for their helpful criticism; Dr. C. A. St. Hill and Miss M. Lichfield for the histological sections; Mr. W. Lee for the photographs and photomicrographs; Miss B. Duckworth for the drawing; and Burroughs Wellcome Ltd. for a supply of crystalline insulin.

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The booklet *Notes on the Diagnosis of Occupational Diseases Prescribed under the National Insurance (Industrial Injuries) Act* is now obtainable by medical practitioners from H.M.S.O. or through any bookseller for 1s. 6d. An earlier edition was issued in 1948 to those medical practitioners to whom claimants to industrial insurance benefit on account of prescribed occupational diseases were being referred for initial diagnosis. Notes on pneumoconiosis and byssinosis have now been added to the booklet.

MORTALITY FROM AND RISK OF GASTRIC CARCINOMA AMONG PATIENTS WITH PERNICIOUS ANAEMIA*

BY

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AND

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The introduction of concentrated preparations of liver and stomach in the treatment of pernicious anaemia (Minot and Murphy, 1926) has changed completely the prognosis of this complaint. The disease, which previously had followed a capricious but usually rapidly fatal course, could now be kept under control, so that as a rule the patients enjoyed a long period of freedom from symptoms with full working capacity.

It is now possible, with more than 20 years' experience of this treatment, to evaluate the prognosis of the disease under the radically altered conditions. While studying for a different purpose a group of patients suffering from pernicious anaemia we arrived at results which differ in several respects from those previously reported and which we therefore feel justified in publishing.

Present Investigations

The series comprises a fairly large number of patients treated for pernicious anaemia at the Bispebjerg Hospital, Medical Department B, during the period 1928 to 1949. A few foreigners and provincials have been omitted. All the case records were reviewed and the diagnoses confirmed according to the following criteria: a characteristic clinical picture, typical blood findings (megalocytic, hyperchromic anaemia, anisocytosis, leucopenia, increase in reticulocytes following specific therapy), and achlorhydria refractory to histamine.

In cases in which the diagnosis had been made before admission to hospital, data regarding the earliest clinical symptoms and blood findings were sought for confirmation. It was decided to leave out one case of megalocytic anaemia in a pregnant woman and two cases in which specific treatment was suspended at the recommendation of the department, since the blood findings were atypical;

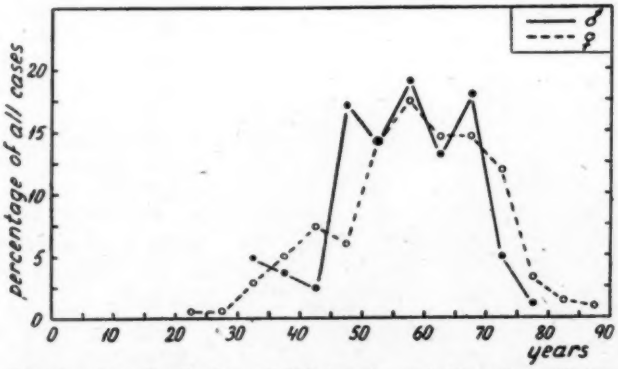

FIG. 1.—Age distribution of 219 females and 82 males suffering from pernicious anaemia. (Age when the disease was diagnosed.)

*This investigation was supported by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service.

one of them has been symptom-free without treatment for 2½ years, but contact with the other has been lost.

Thus curtailed, the series comprises 301 patients—219 females (72.7%) and 82 males (27.3%). Fig. 1 shows the age of the patients when the diagnosis was made (average: females 59.1, males 56.4 years).

Table I groups the series according to the length of the follow-up period, and gives the number of deceased patients within each group.

TABLE I.—*Follow-up Period in 301 Cases of Pernicious Anaemia*

Follow-up Period (Years)	Females		Males	
	Cases	Deaths	Cases	Deaths
1–5	45	32	24	12
6–10 ..	72	26	22	9
11–15 ..	51	16	17	5
16–20 ..	39	7	13	5
21–25 ..	12	2	6	1
Total ..	219	83	82	32

Mortality Among Pernicious Anaemia Patients

The average follow-up period was 10.5 years (10.3 years for males and 10.7 for females), the study being concluded on June 1, 1949. By that time 83 of the 219 females and 32 of the 82 males had died.

On the basis of the mortality among the population of Copenhagen during the period 1935–9, it would be expected that, of 301 individuals of the same age and sex distribution and followed up for the same length of time as the patients with pernicious anaemia, 89 females and 28 males would die. It is evident from Table II that the actual findings are in perfect accordance with the expected deaths, and that in the present series the mortality did not exceed what is normal.

TABLE II.—*Deaths Among 301 Patients with Pernicious Anaemia as Compared with the Number of Deaths Among a Corresponding Group of Normal Persons*

	No. of Deaths Among 301 Patients with Pernicious Anaemia	Expected No. of Deaths
Females	83	89
Males	32	28
Total	115	117

Prognosis

For the purpose of adjudging the actual prognosis in cases of pernicious anaemia the authors chose a follow-up period of 10 years, including in this group only those patients whose disease was diagnosed prior to 1940. This group comprises 222 patients (168 females and 54 males). A total of 51 females and 17 males died during the follow-up period. On the basis of the ordinary mortality it was calculated that, among a population of the same age and sex distribution as the 222 patients, 50 females and 13 males would be expected to die in the course of 10 years.

Figs. 2 and 3 show the survivors among the females and males, respectively, with pernicious anaemia followed up for a minimum of 10 years, and also the survivors among a population of the same age and sex distribution. It is clear from the diagrams that, so far as the females are concerned, the mortality of patients with treated pernicious anaemia is the same as that of the average population. The apparently high mortality among the males (Fig. 3) proves, upon statistical calculation, to be within the error of the mean, due perhaps to chance in this small series of males. In other words, in the present series the life expectancy among the female patients is the same as among normal females; in the case of the males there is a slightly higher, but not significantly excessive, mortality.

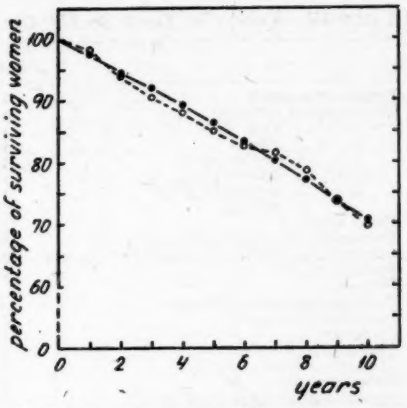

FIG. 2.—Percentage of survivors among 168 females suffering from pernicious anaemia (O- - -O) as compared with the calculated mortality among a corresponding population (●——●).

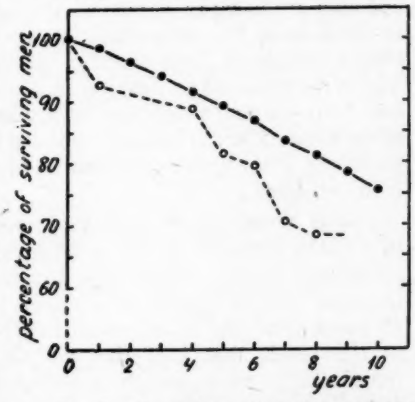

FIG. 3.—Percentage of survivors among 54 males suffering from pernicious anaemia (O- - -O) as compared with the calculated mortality among a corresponding population (●——●).

In contrast to these findings, Jörgensen (1949), in his series of 148 females and 58 males suffering from pernicious anaemia, found the mortality in the females to be 13% and in the males 107% above the normal. He is of the opinion that this high mortality is due entirely to inadequate treatment. The difference in his mortality rate from that of the present series may be due to the fact that our patients were treated largely with the same preparation ("exopylorin," medicinalco), whereas Jörgensen's patients had undergone various treatments. In addition, a large number of our patients have been examined at intervals for years because of the particular interest devoted to pernicious anaemia in the department.

Causes of Death among Pernicious Anaemia Patients

Up to June 1, 1949, 115 (83 females and 32 males) out of the 301 patients had died. Table III shows the way in which the causes of death were ascertained.

TABLE III.—*Sources of the Cause of Death in 115 Cases of Pernicious Anaemia*

	Cause of Death Confirmed by		
	Case Record and Necropsy	Case Record Without Necropsy	Death Certificate
Females ..	13	36	34
Males	7	12	13
Total ..	20	48	47

Sixty-eight patients (49 females and 19 males) died in hospital. In the case of 13 females and 7 males the cause of death was confirmed by necropsy. Forty-seven patients died in their homes, and the cause of death was derived from the death certificates. In cases in which the latter mentioned carcinoma, further details regarding the diagnosis were obtained from the family doctor or the hospital department concerned.

TABLE IV.—*Causes of Death in 115 Cases of Pernicious Anaemia*

	Females	Males	Total	
Pernicious anaemia	2	1	3	(3%)
Carcinoma of stomach	8	6	14	(18%)
" " liver	1		1	
" " colon	1		1	
" " uterine cervix	1		1	
" " thyroid gland	1		1	
" " mammary gland	1		1	
" " prostate		2	2	
Heart disease	23	9	32	(28%)
Pulmonary diseases (apart from cancer)	13	7	20	(17%)
Cerebral disorders (apart from tumours)	19	5	24	(21%)
Pyelonephritis	5		5	(6%)
Uraemia		1	1	
Papilloma of urinary bladder		1	1	
Intestinal obstruction	2		2	(5%)
Peritonitis	1		1	
Cholangitis	1		1	
Cirrhosis of liver	2		2	
Ovarian cystoma	1		1	
Agranulocytosis (due to drugs)	1		1	
Total	83	32	115	

The causes of death in the 115 cases of pernicious anaemia are listed in Table IV. Pernicious anaemia appears to have been the immediate cause of death in only the three cases given. Two of these patients were senile females who were admitted to hospital in a state of severe anaemia, and both were so debilitated that adequate therapy proved of no avail. The third patient refused treatment, and died in his home from severe anaemia a fortnight after discharge from hospital.

In this connexion it might be interesting to call attention to a study from the Simpson Memorial Institute published by Sturgis (1939). Analysing the causes of death in 150 cases of treated pernicious anaemia dying within the first 10 years after the introduction of liver therapy, he arrived at the result that half the patients died from anaemia (particularly myelopathic manifestations with sphincter disturbances) and the other half from irrelevant causes. In the present series myelopathic symptoms did not constitute the cause of death in any case.

Gastric Carcinoma in Pernicious Anaemia Patients

Thirteen females and eight males died from carcinoma (Table IV). On the basis of the mortality from carcinoma among the population of Copenhagen, 1935–9, it may be calculated that, among 301 individuals of the same age and sex distribution and followed up for the same length of time as the anaemic subjects, 6 males and 15 females would be expected to die from carcinoma (Table V). In other words, the mortality from carcinoma among the present series was not excessive.

TABLE V.—*Number of Deaths From Carcinoma Among the Series of 301 Cases of Pernicious Anaemia as compared with the Number of Expected Cancer Deaths*

	No. of Patients	Deaths from Cancer	
		Actual	Expected
Females	219	13	15
Males	82	8	6
Total	301	21	21

It is striking that no fewer than 8 out of 83 females (10%) and 6 out of 32 males (19%) died from carcinoma of the stomach. In addition, the series includes a man who underwent operation for gastric carcinoma and who six months later is still surviving in a debilitated state. Details of the 15 cases of gastric carcinoma are given in Table VI.

Of the females, four died in hospital and were examined at necropsy, but microscopical examination was performed in only one case. Four died in their homes, the diagnoses having been confirmed by characteristic *x*-ray findings, occult bleeding, and the clinical course of the disorder. So far as the males are concerned, histological verification was available from operation or necropsy specimens in five cases. In two cases the diagnoses were substantiated by typical *x*-ray findings. The age stated in the table refers to the age when the diagnosis of carcinoma was made, and, since the patients usually die from carcinoma within the first year (the longest interval in this series being 18 months), the age at diagnosis accords fairly well with the age at death.

TABLE VI.—*Fifteen Cases of Gastric Carcinoma Occurring Among 301 Patients Suffering From Pernicious Anaemia*

Case	Sex and Age	Duration of Pernicious Anaemia Before Gastric Carcinoma was Diagnosed (Years)	Site of Tumour in Stomach	Microscopical Examination
1	F 60	3	Ulcerated tumour occupying entire pyloric area (necropsy)	Papilliferous carcinoma
2	F 71	1	Large tumour occupying distal half of stomach (*x*-ray)	Not performed
3	F 72	2	Flat tumour, size of child's hand, on posterior wall of stomach, 6-7 cm. from pylorus (necropsy)	" "
4	F 72	1	Firm and nodular tumour, size of goose's egg, occupying entire pyloric antrum (necropsy)	" "
5	F 75	15	Entire pyloric area tapers into fine irregular canal (tumour of pylorus) (*x*-ray)	" "
6	F 58	9	Irregular, large filling defects on middle of lesser curvature, reaching to and involving entire cardia (*x*-ray)	" "
7	F 68	17	From fundus a large irregular filling defect extends 8–10 cm. into body (*x*-ray, operation)	" "
8	F 68	4	Ulcerating carcinoma, size of an orange, on middle of lesser curvature (necropsy)	" "
9	M 48	19	Nodular tumour, size of closed fist, on middle of lesser curvature (operation)	Adenocarcinoma
10	M 66	13	Circular carcinoma, size of closed fist, in area of pyloric antrum (operation)	Adenocarcinoma with solid areas
11	M 68	8	Diffuse infiltration of entire stomach (necropsy)	Solid, scirrhous, diffuse carcinoma
12	M 70	7	Firm tumour, size of half-crown, on middle of greater curvature (necropsy)	Adenocarcinoma
13	M 57	5	*X*-ray: pyloric tumour. Operation revealed cicatricial stenosis. Five years later entire stomach was involved in diffuse scirrhous infiltration (operation and *x*-ray)	Not performed
14	M 61	7	Circular constriction of middle area of body which shows irregular, sharp contours. Fundus and pylorus normal (*x*-ray)	" "
15	M 57	14	Operation revealed an ulcerated tumour, size of palm of hand	Adenocarcinoma

All the patients were examined radiologically. Five (one female and four males) underwent operations; necropsy was performed in six instances (four females and two males).

On the average, pernicious anaemia was of eight years' standing (seven years for females and ten years for males) when gastric carcinoma was diagnosed, the average age when the carcinoma was diagnosed being 68 years for the eight females and 61 years for the seven males. This difference in age is not statistically significant, but in all probability it is real, since Jörgensen found a corresponding sex difference in his series.

On the basis of the ordinary mortality from gastric carcinoma among the population, corresponding as regards sex and age to the 301 cases of pernicious anaemia and followed up for the same length of time, it may be calculated that 3.5 females and 1.7 males should have died from

TABLE VII.—*Incidence of Gastric Carcinoma Among 301 Cases of Pernicious Anaemia as Compared with the Expected Incidence in a Corresponding Normal Population*

	No. of Patients	Cases of Gastric Carcinoma	
		Occurring	Expected
Females ..	219	8 (4%)	3·5 (1·6%)
Males	82	7 (9%)	1·7 (2·1%)
Total ..	301	15 (5%)	5·2 (1·7%)

gastric carcinoma at the end of the follow-up period. Table VII gives the cases of gastric carcinoma occurring in the present series as compared with the expected incidence.

The number of patients dying from gastric carcinoma in the present series has thus far exceeded the expected deaths. The difference is significant for females as well as for males. It strikes one that the increased incidence of gastric carcinoma does not involve a corresponding increase in the incidence of total carcinoma.

Previous workers (Jenner, 1939; Waldenström, 1945; Kaplan and Rigler, 1945, 1947; Bourne, 1948) have called attention to the particular predisposition to gastric carcinoma among patients suffering from pernicious anaemia. This finding was recently confirmed by Jörgensen, who emphasized that the increase in the incidence of gastric carcinoma among patients suffering from pernicious anaemia was more marked among males than among females, an observation which accords with the findings in the present series. It is difficult to explain this male preponderance. The data available in our series afforded no evidence that the male patients developing gastric carcinoma were alcohol addicts.

Attempts have been made to explain the high incidence of gastric carcinoma in association with pernicious anaemia as being the result of the pathological changes found in the stomach in the latter condition. It has been pointed out by Meulengracht (1939) that patients with pernicious anaemia are affected with atrophic gastritis, localized primarily to the fundal area, whereas the mucosa of the distal part of the stomach is comparatively intact. If this gastritis were the precursor of gastric carcinoma, such carcinoma would be expected to develop by preference in the fundal area or at least in the proximal part of the body.

According to Torgersen (1944) gastric carcinoma in pernicious anaemia is in the great majority of cases localized to the fundus and to the proximal part of the body. In contrast, gastric carcinoma in a non-selected material was found to be situated in the pylorus and pyloric antrum in 50 to 60% of the cases. Torgersen's series comprises 106 cases of pernicious anaemia coexisting with gastric carcinoma (90 from the literature and 16 of his own). According to the description, in only two of his own cases was the carcinoma unmistakably in the fundus, whereas in seven it was in the body and in seven in the pylorus.

There seems to be some incongruity between Torgersen's observations in his own cases and the conclusion which he claims to be able to draw from earlier reports. The earlier reports of gastric carcinoma in association with pernicious anaemia have usually been of single cases or of groups comprising only a few patients. Among a somewhat larger series (Table VIII), the one reported by Strandell and Jansson (1937) is worth mentioning. Among 686 cases of pernicious anaemia they found 21 of gastric carcinoma in the following sites: nine in the pylorus, four in the fundus, and eight in the body of the stomach.

TABLE VIII.—*Site of Gastric Carcinoma Occurring in 85 Cases of Pernicious Anaemia*

	Pylorus and Antrum	Body	Fundus	Diffuse
Jenner (1939)	3	2	1	1
Strandell and Jansson (1937)	9	8	4	
Washburn and Rozendaal (1938)	4	2	3	
Torgersen (1944)	7	7	2	
Doehring and Eusterman (1942)	8	4	3	2
Present series	5	6	2	2
Total ..	36	29	15	5

Among 906 cases of pernicious anaemia Washburn and Rozendaal (1938) found gastric carcinoma in nine—three were in the fundus, two in the body, and four in the pylorus.

Jenner (1939), studying 181 cases of pernicious anaemia, found among them seven cases of gastric carcinoma. In one case the fundal area was definitely the site of the tumour; in two cases the site was probably the body; in three it was natural to interpret the tumour as being in the pylorus; and in the last case the growth was without doubt a scirrhus involving the entire stomach.

Doehring and Eusterman (1942) found 17 instances of gastric carcinoma among 1,014 patients suffering from pernicious anaemia. Eight were situated in the distal third of the stomach, four in the middle third, and three in the proximal third; two cases involved the entire stomach. These authors concluded that the site of gastric carcinoma in patients suffering from pernicious anaemia did not differ from that found normally.

The reported cases of gastric carcinoma in the presence of pernicious anaemia therefore fail to afford evidence that the growths in these patients are situated by preference in the fundal area or in the proximal part of the body.

The present series includes five cases of pyloric carcinoma, six of the body, and two of the fundus; in two instances the entire stomach was involved. Accordingly, this group does not confirm the theory that gastric carcinoma in the presence of pernicious anaemia should be localized by preference to the fundus.

The reason for the particular predisposition to gastric carcinoma among patients suffering from pernicious anaemia remains unelucidated. Possibly the explanation is that both pernicious anaemia and gastric carcinoma result from achlorhydria. If so, it is not unnatural that the two conditions should at times coexist. There is perhaps a question of inherited factors, since achlorhydria, an almost invariable sign of both lesions, occurs with particular frequency in families affected with pernicious anaemia.

A wide study of the familial occurrence of achlorhydria, pernicious anaemia, and gastric carcinoma may help in elucidating the relationship between these lesions. Investigations along these lines are being carried out.

Summary

A total of 219 females and 82 males who received treatment for pernicious anaemia at the Bispebjerg Hospital, Medical Department B, Copenhagen, during the period January, 1928, to June, 1949, have been studied. Of these, 83 females and 32 males have died. The expected number of deaths is 89 females and 28 males.

Two hundred and twenty-two patients have been followed up for more than ten years. Female patients with pernicious anaemia have the same chances of survival as normal females, whereas there is a slightly but not significantly higher mortality among the males.

The causes of death are tabulated. Twenty-one patients died from carcinoma, a figure which corresponds to the expected number of cancer deaths. Among this group, however, no fewer than eight females and six males died from gastric carcinoma. The expected number of deaths from carcinoma in all sites is 15, from gastric carcinoma only 5, so that the excessive mortality from gastric carcinoma is statistically significant.

It is found that patients suffering from pernicious anaemia do not develop their gastric carcinoma in the fundus and upper part of the body of the stomach, where the pathological changes characteristic of pernicious anaemia are localized. Possibly the explanation is that both pernicious anaemia and gastric carcinoma result from achlorhydria.

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HAEMOLYTIC STREPTOCOCCAL GANGRENE OF BREAST SUCCESSFULLY TREATED WITH STREPTOMYCIN

BY

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Haemolytic streptococcal gangrene was first accurately described by Meleney (1924). In almost all cases there is an initial lesion which may escape the patient's notice. The limbs are affected more commonly than any other part of the body, as they are exposed to injury. The disease may occur in the scrotum (Marcus, 1949) and rarely on the trunk. Its clinical course is characterized by very rapid development. Within twenty-four hours the affected part becomes markedly swollen and shows all the signs of a rapidly spreading inflammation. In a day or two blisters and bullae begin to form and then the skin becomes frankly gangrenous. The condition is due to the haemolytic streptococcus, which can be obtained by culturing the discharge aerobically or anaerobically. Other organisms, such as *Staphylococcus aureus, Pseudomonas pyocyanea, Bact. coli, Proteus vulgaris, Streptococcus faecalis*, and diphtheroids may occur as secondary invaders.

Meleney (1924) recommends incision as far as the extension of the subcutaneous necrosis, but not further, as incisions in the zone of cellulitis may be harmful. The gangrenous skin should be excised as soon as the line of demarcation has developed and removal can be adopted without causing much bleeding. Amputation is rarely necessary, as the infection is superficial in most cases and can usually be combated by superficial incisions.

Penicillin and the sulphonamides have proved of value in haemolytic streptococcal infections, and in many cases render incisions unnecessary. The following two cases may be of interest, as these drugs failed to prevent the infection spreading, but when used with streptomycin localization occurred within a few hours.

Case 1

A married woman aged 57 was admitted for investigation for Cushing's syndrome. She had a small infected area on the left breast, for which she was given 100,000 units of penicillin daily. The inflammation extended by 1¼ in. (3.8 cm.) in 24 hours and discharged copiously. When seen five days later the skin of the breast, except for the nipple and areola, was gangrenous (Fig. 1). The spreading margin extended upwards towards the clavicle, and was painful and vesiculated. Sulphatriad, 1 g. thrice daily, was given for 48 hours.

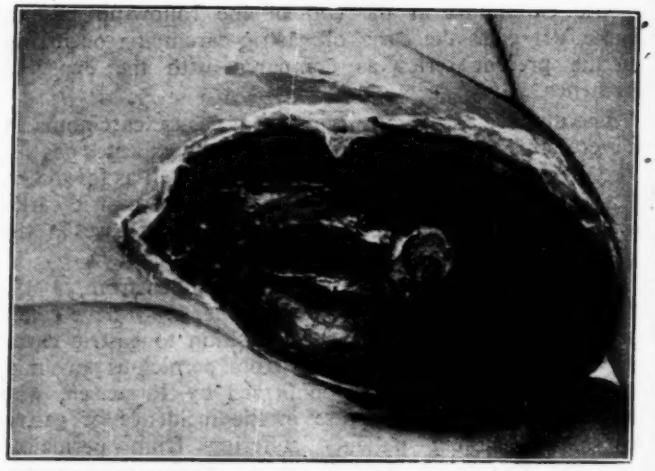

FIG. 1.—Case 1. Before streptomycin. The skin of the breast is gangrenous, and the gangrenous process is extending by 1¼ in. daily.

Culture on February 16 showed: haemolytic streptococcus sensitive to 1/16 unit of penicillin per ml. and 8 units of streptomycin per ml.; *Staph. aureus* sensitive to 32 units of penicillin per ml. and 2 units of streptomycin per ml. Streptomycin, 0.5 g. six-hourly, was given—total 6 g.

The general condition improved within 12 hours. The tenderness was lessened, the spreading process was arrested, and the gangrenous skin showed a line of demarcation. Culture: haemolytic streptococci sensitive to 1/16 unit of penicillin per ml. and 8 units of streptomycin per ml.; *Staph. aureus* resistant to at least 32 units of penicillin per ml. and sensitive to 4 units of streptomycin per ml.

On February 18 the bacteriological findings and sensitivity to penicillin and streptomycin were unaltered. About three-quarters of the gangrenous skin had separated, and this was easily cut away with scissors, leaving a remarkably clean granulating surface. The remainder of the skin was removed next day without causing much bleeding; the nipple and areola were left intact. A small area below the nipple was affected more deeply than the remainder of the breast and contained a slough about ¼ in. (1.9 cm.) long. Culture from this region grew *Proteus vulgaris*.

On February 23 healing began, and granulations were healthy except for a small area below the nipple. Culture from this region grew *Proteus vulgaris* resistant to at least 32 units of penicillin. On March 23 postage-stamp Thiersch grafts were applied to the granulating surface. By April 1 most of the grafts had taken successfully and healing proceeded rapidly. The raw area had completely epithelized by April 18.

Comment on Case 1

The haemolytic streptococcus isolated was of Lancefield Group A. It was not completely eliminated from the margin of the gangrenous area during the period streptomycin was given. After the gangrenous skin had been removed the organisms were not found in repeated cultures from the margin of the granulating tissue. As the skin was not viable when streptomycin treatment was initiated

it is not surprising that the organisms were not eliminated until the affected area was excised.

Case 2

A married woman aged 64 had a radical mastectomy for carcinoma of the breast. The wound had been sutured without tension. Five days after operation she was toxic and had severe pain in the wound. There was a small area of erythema with a vesicular centre in the outer part of the wound. She was given 500,000 units of penicillin intramuscularly daily and 1 g. of sulphadimidine three times a day.

When seen 14 hours later the temperature was 103° F. (39.4° C.), pulse 180. The outer part of the incision showed a gangrenous area, undermining of the skin, and gross oedema. While being examined the margin was seen extending. The discharge from the wound was copious and foul-smelling. Culture from the margin grew anaerobic haemolytic streptococci sensitive to one unit of streptomycin per ml., *Staph. albus* (coagulase-negative), and an organism of *Bacillus subtilis* group. Streptomycin, 0.5 g. six-hourly, was given—total 6 g. Sulphadimidine was discontinued, as this caused vomiting.

Next day her general condition improved considerably; the tenderness was much less and the spreading margin was arrested. The following day the gangrenous skin showed a line of demarcation and was excised (Fig. 2). Cultures grew

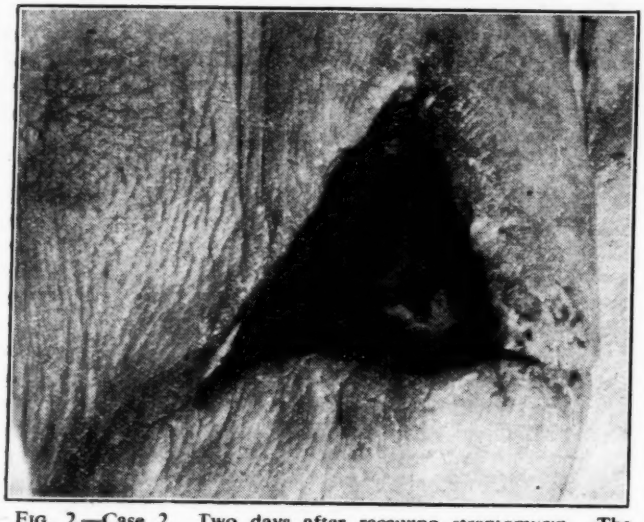

FIG. 2.—Case 2. Two days after receiving streptomycin. The gangrenous skin showed a line of demarcation and was excised. The sutures have been removed and the remainder of the incision has healed. Pain and oedema were markedly decreased.

anaerobic haemolytic streptococci, non-haemolytic streptococci, and an organism of *B. subtilis* group. A week later the wound was dry and healthy. Closure was carried out with interrupted sutures, and a small stab drain was inserted into the dead space below the suture line.

Discussion

Meleney (1933) classified the various types of infectious gangrene of the skin as acute and chronic. The acute forms are represented by gas gangrene and haemolytic streptococcal gangrene; the chronic forms include ecthyma (gangrenous impetigo), anaerobic gangrene, fuso-spirochaetal gangrene, and progressive bacterial synergic gangrene. The last-named condition is due to a symbiotic infection by a non-haemolytic *Staph. aureus* (Brewer and Meleney, 1926; Meleney, 1931, 1933, 1935). There are a few reports of successful treatment of post-operative progressive bacterial synergic gangrene with penicillin (Grimshaw and Stent, 1945; Meleney *et al.*, 1945; Clarke, 1947). In successful cases the inflammation, induration, oedema, and pain around the wound resolve and healing occurs rapidly, or after skin-grafting. Failing a satisfactory response excision of the wound is necessary before the condition is finally controlled (Meleney *et al.*, 1945).

Haemolytic streptococcal gangrene has been described as phlegmonous or gangrenous erysipelas, but should not be confused with erysipelas, which is also caused by the haemolytic streptococcus. Lymphangitis and lymphadenitis are rare, though phlebitis is fairly common in the former condition. In erysipelas, organisms may be cultivated at and beyond the spreading margin but not in the centre. The reverse is the case in haemolytic streptococcal gangrene. There may be a wide zone of sterile oedema beyond the limits of necrosis.

The synergic effect of penicillin, streptomycin, and the sulphonamides is of value when one drug alone fails to arrest the gangrenous process. This synergic effect has been noted in other infections (Redewill and Potter, 1948; Wells and Marcus, 1949; Bigger and Daly, 1949). The response to this form of treatment in the above two cases was dramatic. Within a few hours there was demonstrable improvement in the local and general condition of the patients. The spreading process was arrested and separation of the gangrenous skin began before completing streptomycin therapy. In both cases incisions as recommended by Meleney (1924) were not necessary.

The morbidity resulting from anaerobic streptococcal gangrene may be decreased by early recognition of the condition and by giving streptomycin before the gangrenous process is extensive. Incisions and skin-grafting will then be unnecessary. It is questionable whether secondary sutures are as valuble as skin-grafting. The undermining of the skin results in a dead space which cannot be easily obliterated by sutures.

Summary

Two cases of streptococcal gangrene of the breast are described. Penicillin and the sulphonamides by themselves failed to prevent the infection spreading, but when used together with streptomycin this was localized within a few hours.

Grateful thanks are due to Professor C. A. Wells and Mr. H. Hughes, who entrusted me with the care of their patients. I also thank Professor A. W. Downie and Dr. T. Black for the bacteriological investigations and sensitivity tests, and Mr. W. Lee, of the Central Photographic Department, University of Liverpool, for the illustrations. The streptomycin used for Case 1 was supplied by the Medical Research Council.

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Normally claims for sickness benefit must be made within three days of the beginning of an illness, but when a person has never claimed sickness benefit before there will be no penalty so long as the claim is made within 21 days of the beginning of the illness. This is the main effect of provisional regulations made by the Minister of National Insurance, Dr. Edith Summerskill, which came into force on July 19. The regulations also enable delay in making a claim to be automatically excused during a period in hospital up to a maximum of three months. There is no change in the general rule that sickness benefit cannot be paid for more than three days before the claim is received at the local National Insurance office unless good cause for the delay is shown. The new regulations, however, allow late claims to be accepted without inquiry into the reason in special circumstances where difficulty has been experienced by insured persons.

RHEUMATIC HEART DISEASE IN SERVICE PENSIONERS

A REVIEW OF 318 CASES

BY

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During the 1939–45 war cardiologists recorded their experience in the diagnosis of early chronic rheumatic heart disease in recruits. In spite of excellent work by medical boards, backed by specialist opinion, a small proportion of men with this condition were accepted for service. This paper reports the subsequent course of 318 such men re-examined after discharge while drawing disability pensions. In only one of these had the opinion of a cardiologist been taken before entry. The age at diagnosis varied from 18 to 50, and it may be presumed that the disease was already present on entry, for all had well-established valvular disease at the time of diagnosis. The lesions present are shown in Table I. In only five cases had an apical systolic murmur been noted on entry. In view of the fact that many hundreds of men with incidental systolic murmurs were accepted for service on specialist advice it is apparent that clinically the problem of distinguishing incidental from organic systolic murmurs has been largely solved. At the time of invaliding three of these five had mitral stenosis and aortic incompetence and two had mitral stenosis only. Seven other men had hypertension in addition to the valvular lesion.

TABLE I.—*Incidence of Clinical Valvular Disease Found in 318 Men at Time of Diagnosis*

Mitral stenosis	82 (25·7%)
Aortic incompetence	77 (24·2%)
Mitral stenosis and aortic incompetence	127 (39·9%)
Aortic stenosis and incompetence	19 (5·9%)
Mitral stenosis, aortic incompetence, and aortic stenosis	13 (4·0%)

After the 1914–18 war Grant (1933) analysed 736 cases invalided with valvular heart disease, and his figures show aortic lesions in nearly 60%, compared with 74% in this series. Both these figures were high and do not represent the true incidence of aortic valvular involvement, for aortic valvular disease is more readily missed than mitral valvular disease in routine examination, and so those with aortic lesions are more likely to enter the Forces, yet rheumatic aortic lesions are far commoner than is generally realized.

A history of previous rheumatic infection was obtained in only 37% in this series—a low figure; 100 men reported an attack of rheumatic fever, 15 of chorea, and 3 of both diseases.

Medical boards were much influenced by such a history, and many men were referred to cardiologists for this reason alone. This largely explains the low percentage of positive histories in this valvular series.

The features leading to diagnosis are given in Table II.

TABLE II.—*Features Leading to Diagnosis in 318 Men With Chronic Rheumatic Heart Disease*

Rheumatic fever	98 (31%)
Dyspnoea on effort	73 (23%)
No symptoms. Discovered at routine examination	104 (33%)
Haemoptysis	17
Anxiety state	7
Onset of auricular fibrillation	5
Mass radiography	3
Bacterial endocarditis	4
Congestive cardiac failure	1
Paroxysmal tachycardia	1
Embolic phenomena	1
Angina of effort	2

Cases with Recurrence of Rheumatic Fever.—The expected recurrence rate of rheumatic fever at the age of 20–25 is approximately 5% (Wilson, 1940). A Service rate of 31% is very high. Although a few men were under active service conditions when they had their relapse, most admitted that they were in good billets. It was apparently the open-air life and exposure to chill during training that brought about so many relapses. There was an increased liability to relapse in those who had had a previous known attack. In this group 51% relapsed within two years of enlistment, while only 13% served over five years. The valve affected in the 98 patients who developed acute rheumatic fever in the Service was the aortic in 35 (36%), the mitral in 18 (18%), and the combined lesion in 45 (46%). This is surprising, but the figures are hardly adequate for definite conclusions to be drawn. A previous rheumatic history was recorded in 50% of these men. There was no difference in the age at relapse between those with such a history and those without it.

Cases Reporting with Dyspnoea.—Only 27.4% of these men had a previous rheumatic history. The age at which the symptom appeared is that which would be expected from present knowledge of the natural history of the disease. There is no evidence that it was precipitated prematurely by the vigorous Service training. In this group 42% reported dyspnoea within two years of enlistment, while 27% served over five years.

Cases Diagnosed on Routine Examination.—A previous rheumatic history was recorded in 31%. The diagnosis in 16 was made at the demobilization examination. The percentage of men with a cardiac neurosis superimposed upon their disability is high. This is due to a failure on the part of doctors to explain the condition to the patient at the first diagnosis. Too often a man's sole knowledge about a cardiac affection is derived from the more sensational novels and films. Among the 104 men diagnosed on routine examination, all denying dyspnoea prior to diagnosis, over 80% claimed the advent of their symptoms within six months of diagnosis. This is due to two facts: first, the development of cardiac neurosis, and, secondly, the over-restriction of activities. All 104 had done their full Army training—the majority one battle course and a high percentage two or more such courses—yet they had no dyspnoea until they were told to go carefully. Lack of training alone may account for this symptom. A history of collapse or heart failure during exercise was not found among these 104 men or among the 73 reporting with dyspnoea.

Cases with Haemoptysis.—The percentage presenting with an initial haemoptysis was small—17 men (5.3%). In most cases there was prolonged dyspnoea as a result of work in full kit or wearing gas masks before haemorrhage occurred. The great importance of haemoptysis as a symptom of mitral stenosis does not seem to be fully appreciated. Often there was considerable delay while lung investigations were carried out and before the correct diagnosis was made. Five men entered sanatoria; one of these had four postero-anterior *x*-ray plates of the chest taken before the true condition was recognized.

Cases with Bacterial Endocarditis.—The percentage of men with subacute bacterial endocarditis in this series is low and many must have died from the disease before the introduction of penicillin. Those who survived were permanently disabled and none were fit for work.

Discussion

That most of the 318 cases could have been diagnosed before entry is without question. Twelve admitted that they were rejected as volunteers and later were accepted as conscripts. One man was invalided from the Guards and

then joined the Royal Air Force. These keen men persevered until they had their own way, and came to no harm while doing excellent service.

Failure to carry out a full clinical cardiac examination such as recommended by Parkinson and Hartley (1946) accounted for most acceptances. In many men auscultation failed to reveal the mitral diastolic or presystolic murmur with the patient in the standing position, when these conditions were obvious with the man lying in the left lateral position after exertion. In the same way many aortic diastolic murmurs could be heard only when the breath was held at the end of full expiration with the patient sitting. But there is often a silent period in the natural history of rheumatic fever when no murmurs may be present, and in the absence of radiological enlargement a positive diagnosis is impossible. The early diastolic murmur of aortic incompetence may be difficult to hear unless there is absolute quiet, and many boards did not work under such ideal conditions. Boards were handicapped by the absence of facilities for routine radioscopy and so depended entirely on the clinical findings.

More attention might have been paid to the apex beat. The apex beat as a physical sign has two components—position and type of impulse. The position is defined as the furthermost point outwards and downwards at which the impulse raises the examining finger. This point is an extremely accurate guide to the left cardiac border, except in those with a broad chest and those with a vertical heart. Normally the position lies within the mid-clavicular line. Among these 318 men both position and character were normal in only 20. In 154 the position was normal but the type of impulse was diagnostic : mitral stenosis gives a sudden impulse, aortic incompetence a forcible one. Over 200 normal young Naval officers were examined as a control, and in none was the type of impulse abnormal, while in only two was the position beyond the mid-clavicular line. These were both broad short men, and the coincidence of the apex beat as defined above with the radiological left border of the heart was confirmed in these officers.

Radiology

The radiological findings of established chronic rheumatic heart disease are well known, and the use of mass radiography in the future will ensure that most men with the disease will not be accepted for military service (Maclean and Rogen, 1949). It will not exclude all. The limitation of mass radiography in heart disease is that the postero-anterior film only is taken, whereas the earliest change in mitral stenosis is enlargement of the left auricle, shown in the right oblique position with barium in the oesophagus.

Parkinson and Hartley (1946) found this to be the only certain *x*-ray change in 74% of 104 symptomless recruits with presystolic murmurs, while in 13% there was no change in the size or shape of the heart. The same observers could find no change in the heart's appearance in 16% of 202 men with symptomless rheumatic aortic incompetence. Full-plate radiographs, usually only postero-anterior, were taken of 264 men in this series at the time of the first diagnosis. Of these, 215 hearts (81.4%) were reported as enlarged, while 44 (16.6%) were reported as normal. The valvular lesions found in these 44 men are shown in Table III. The high percentage of radiographs reported to be normal in this series is discouraging, for if enlargement is not detected on the full-size plate it is unlikely to be recognized on the miniature film. Five more (1.9%) were diagnosed on mass radiography. Three of these had mitral stenosis, one aortic incompetence, and one both.

TABLE III.—*Valvular Lesion in 44 Men Whose Postero-anterior Film Was Reported as Normal at the Time of Clinical Diagnosis*

Mitral stenosis	8
Aortic incompetence	13
Mitral stenosis and aortic incompetence	19
Mitral stenosis, aortic incompetence, and aortic stenosis	2
Aortic incompetence and stenosis	2

It is during the silent period of the disease that radiology is the only method of detection. Wilson (1940) says that, in her patients, while the auscultatory signs of cardiac involvement might disappear or become uncharacteristic during the course of the disease, cardiac enlargement was demonstrable at all times. Hartley (1948) has pointed out that aortic incompetence may cause enlargement before the aortic diastolic murmur is heard, while, as Parkinson (1949) has emphasized, the *x*-ray appearance often suggests further auscultation, with positive results.

It has always been well known that the patient with a chronic rheumatic heart fares badly in the armed Forces. He should not be accepted, as it is impossible to foresee which case will deteriorate and which will not.

The figures in Table I show that men with chronic rheumatic heart disease who are accepted for the Forces fall mainly into three groups from the medical point of view.

In the first group there occurred during service some incident of the rheumatic disease which might be expected to affect permanently the natural history of the disease in that man. Such incidences are the recurrence of rheumatic fever, auricular fibrillation, bacterial endocarditis, heart failure, angina of effort, or embolic phenomena. In all these cases, although such complications might have occurred in civilian life, the prognosis has been made worse. Hence a permanent increase in the disability must be accepted as a medical fact. Of the 318 men 34% are found in this group.

In the second group fall those men whose initial symptoms occurred during service, but in whom there was no specific incident that might be expected to influence the ultimate prognosis. Dyspnoea was the main symptom. Haemoptysis in 17 cannot be said to have done any permanent damage. Paroxysmal tachycardia is a disorder of function only. Nearly 29% fell in this second category. The presenting symptom can in no way be associated medically with military service, for between the ages of 20 and 30 the onset of symptoms is to be expected.

The remaining third of the cases had no symptoms before the diagnosis at routine examination. Over 80% of these developed dyspnoea within six months of this knowledge. It would appear that Service life with daily exercise improved their condition, and allowed them to exert themselves more than they would have been able to do otherwise.

It was the overrestriction of their activities, together with inadequate knowledge of their own condition, that precipitated symptoms.

Summary

Of the 318 men drawing disability pensions for chronic rheumatic heart disease who were re-examined, 74% had an aortic-valve lesion.

Only five men had an apical systolic murmur on entry, and the conclusion is drawn that the many hundreds of men accepted with incidental apical systolic murmurs were correctly assessed and so provide remarkably few of the cases here examined.

Most of the cases (87%) were revealed in three main ways —31% had a recurrence of rheumatic fever, 23% developed dyspnoea, and 33% were discovered on routine examination. These three groups of cases are discussed in detail.

The reasons why medical boards failed to diagnose and exclude these cases from service are discussed, with special reference to the importance of the position and type of the apex beat in diagnosis.

Increased disablement from a purely medical point of view occurred in only 34% of the total. It was caused by recurrent rheumatic fever, bacterial endocarditis, auricular fibrillation, angina of effort, and the occurrence of emboli or cardiac failure.

The importance of radiological examination of the heart and the potential value of mass radiography are discussed.

I wish to thank Sir John Parkinson for his helpful criticism. My thanks are also due to Dr. F. T. Rees, Director-General of Medical Services, Ministry of Pensions, for permission to publish this article, which does not necessarily represent the view of that Ministry.

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DECAMETHONIUM IODIDE AS A CURARIZING AGENT IN GENERAL ANAESTHESIA

BY

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The following series of 208 cases in which decamethonium iodide (C10) was used as a curarizing agent, in conjunction with most general anaesthetic agents, may prove of interest to those who are not convinced of its value as a substitute for D-tubocurarine chloride.

C10 is the decane derivative of bistrimethylammonium iodide. It is a white crystalline water-soluble salt, which forms a stable neutral solution. On intravenous injection both in experimental animals and in human beings it produces a neuromuscular block with little or no effect on the autonomic ganglia. The fact that it is cheap to synthesize and mixes readily with thiopentone sodium, together with its curarizing properties, makes it an even more attractive proposition.

Clinical Series

In all the 208 cases, with the exception of those in which caesarean section was performed, premedication with "omnopon," ¼ gr. (22 mg.), or morphine, ¼ gr. (16 mg.), and hyoscine, 1/150 gr. (0.43 mg.), or atropine, 1/100 gr. (0.65 mg.), was carried out between 30 and 60 minutes before operation, and anaesthesia was induced with thiopentone sodium in doses varying from 0.4 to 1 g. For the caesarean sections premedication was carried out with atropine, 1/100 gr., and induction with cyclopropane and oxygen. The ages of the patients ranged from 12 to 79 years. The following are the operations for which the method was used.

Operation	No.
Oesophagoscopy	10
Bronchoscopy	5
Tonsillectomy	18
Mastoidectomy	10
Thyroidectomy	8
Dental operations	20
Facial and neck operations	13
Upper abdominal operations (including gastrectomy, gastro-jejunostomy, perforated peptic ulcers, cholecystectomy)	14
Laparotomy (appendicectomy, colostomy, excision of colon, etc.)	9
Herniorrhaphy	21
Prostatectomy	10
Nephrectomy	4
Anal and rectal operations	12
Thoracic sympathectomy	4
Caesarean section	13
Mastectomy	3
Amputation of leg	3
Laminectomy	10
Orthopaedic, unclassified	11
Unclassified, miscellaneous	10

Administration and Results

C10 may be injected intravenously either as a mixture with thiopentone sodium or by itself. Dosages of from 2 to 5 mg. have been used on different cases, and to produce full muscular relaxation an initial dose of 4 mg. was found to be the best. This produced excellent relaxation of the abdominal musculature for as long as 25 minutes, but also brought about apnoea due to respiratory paralysis for five to ten minutes after the full effect was obtained, which was usually some three to five minutes after the original injection.

Experiments carried out on the conscious patient by Organe, Paton, and Zaimis (1949) indicated that with a dose of 3 mg. of C10 the respiratory musculature was not in any way affected. It has been found here, however, that even with this dose there was apnoea for one to three minutes, while adequate abdominal relaxation was not always obtained. In this respect it differs from D-tubocurarine chloride, which does not always produce respiratory arrest with an equivalent dosage.

Repeated doses have not the cumulative effect that D-tubocurarine chloride has, and a maximum of 15 mg. of C10 has been given without ill effects, recovery taking place as after a single dose.

Continuous or intermittent injections of a thiopentone C10 mixture have been used with success in most of the herniorrhaphies and in a large number of the intraperitoneal operations, but the resulting apnoea makes it desirable to intubate these patients and to keep them well oxygenated.

The experimental work of Young (1949) on near-term guinea-pigs and rabbits suggests that C10 does not pass the placental barrier, and clinical trials by Organe (1949) indicate that this is so. In the 13 caesarean sections in this series, using doses of 2 to 3 mg. injected 10 to 15 minutes before delivery, we have found that the infant was definitely more flaccid and reluctant to breathe than after cyclopropane, oxygen, ether, or gas-oxygen-ether anaesthesia. It would seem, then, that C10 does cross the placenta into the foetal circulation, although more slowly and in smaller quantities than D-tubocurarine chloride. Recovery of muscle tone in these babies is fairly rapid.

Side-effects.—No deleterious side-effects were noted in any of these cases. One death occurred at the end of a partial gastrectomy for uncontrollable haematemesis. This patient was not, however, in the best condition, and some difficulty was experienced in keeping him oxygenated. Post-mortem examination revealed bilateral basal pneumonitis, with a large amount of purulent exudate and an advanced degree of myocardial degeneration.

Discussion and Conclusions

The use of C10 in short operations is clearly indicated to avoid the respiratory depression so often seen after the use of D-tubocurarine chloride. In all cases in which

intubation is necessary or desirable C10 facilitates the passage of a Magill intratracheal tube without producing complete abdominal relaxation, which is so often unnecessary in E.N.T., orthopaedic, and other classes of operation.

It may be used in conjunction with D-tubocurarine chloride to produce short-term relaxation of the abdominal muscles when the peritoneum is being closed and it is undesirable to give another dose of D-tubocurarine chloride because of its long action and cumulative effect. Full respiratory excursions will then be established before the patient returns to the ward.

Antagonist.—Pentamethonium iodide, or C5, is the antidote to C10. Hewer *et al.* (1949) have reported its effects. It acts by producing a block of the autonomic ganglia, and would seem to be contraindicated in major surgery. It may produce a profound fall in blood pressure, and the patient may collapse in a very alarming manner. No opportunity has arisen and no attempt been made to use this substance here.

My thanks are due to Dr. T. H. Hobbes, the senior anaesthetist, for his help.

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Medical Memoranda

Volvulus of the Small Intestine

The following case illustrates the difficulty of diagnosis of volvulus of the small intestine. This difficulty is present not only before operation but when the abdomen has been opened. The aetiology of the condition is obscure, and in the case described an adhesion was present round which the gut appeared to have pivoted. This has been described in other cases, but the operator is likely to find no obvious cause whatever.

CASE REPORT

A storekeeper aged 53 was admitted to hospital complaining of acute abdominal pain 1 in. (2.5 cm.) to the left of the umbilicus two days previously. Before this he had always been quite well. There was continuous dull abdominal pain with exacerbations of acute colic. The bowels had been absolutely confined and no flatus passed. Vomiting began a few hours after the onset of pain and had continued.

On admission he had an ashen appearance. His tongue was dry and furred. His temperature and pulse were normal. The abdomen was tympanitic and a little distended but with no real rigidity. No free fluid was discovered and there were no localizing signs of any sort to assist diagnosis. He was vomiting brownish fluid but there was no faecal change in the vomit. Enemas were returned unchanged. Borborygmi were heard over the large intestine. A diagnosis was made of small-bowel obstruction probably due to strangulation by band or internal hernia.

At operation there was a little free fluid and the whole small intestine presented moderately distended and markedly congested but not "plum coloured." In the left hypochondrium a band 3/16 in. (0.5 cm.) in diameter and extending from the splenic flexure downwards and inwards was found to be attached to the middle of the mesentery. This band was part of numerous adhesions tying the whole colon from caecum to sigmoid to the anterior peritoneum. The small intestine was free of adhesions. The large intestine was moderately and normally distended. Round the band was wrapped a loop of small intestine which was more obviously affected than the rest, as it was plum coloured and more distended. The band was divided and the small loop began to recover in appearance. At first it was thought that the cause of the obstruction had been discovered and dealt with, but the poor condition of the whole small intestine raised doubts, and, on feeling round the abdomen, the typical "band" caused by the twisted mesenteric root was felt and the volvulus diagnosed. The small intestine was eventrated, the 180-degrees twist that was present was untwisted, and the abdomen closed. The patient made an uninterrupted recovery.

A. J. HOBSON, F.R.C.S.

Aplastic Anaemia Complicating Miliary Tuberculosis

In the following case complete aplasia of the bone marrow developed. This seems to be an unusual complication and the clinical findings are worth recording.

CASE REPORT

The patient, a man aged 41, was healthy until March, 1949. His initial symptoms were non-specific—namely, lassitude, anorexia, and headaches. In June, 1949, he had a severe epistaxis and bleeding from the gums. He was admitted to hospital on August 4. There was no family history of tuberculosis.

On examination he was obviously very ill. He complained of a sore throat. The fauces were injected but not ulcerated. Pallor was pronounced without any evidence of icterus. The superficial lymphatic glands were not enlarged. His temperature was 101.6° F. (38.7° C.) on admission, and a remittent pyrexia, fluctuating between 100 and 103.2° F. (37.8 and 39.6° C.), persisted until the day before death. The pulse was 120. A loud systolic murmur was audible at the mitral area. The blood pressure was 145/80. No abnormal signs were elicited in the lungs. The spleen was enlarged to ½ in. (1.2 cm.) below the umbilicus, and the liver was enlarged 2 in. (5 cm.) below the costal margin.

The urine was normal. A blood count showed: haemoglobin, 36%; red cells, 1,510,000; C.I., 1.2; white cells, 1,200. No primitive cells were seen in the film. The red cells showed anisocytosis and poikiloeytosis. Aerobic blood culture was negative. Examination of the sternal marrow smears revealed no primitive cells of either the myeloid or erythrocyte series. The film was diagnostic of aplasia of the bone marrow.

A radiograph of the chest showed a resolving area of consolidation in the left mid-zone. The remainder of the lung fields was clear. There was no enlargement of the mediastinal lymph nodes and no mottling. The patient died on August 21, 17 days after admission.

Permission for a necropsy could not be obtained, but the spleen was removed. This viscus was grossly enlarged and the histological examination showed multiple areas of necrosis with a slight mononuclear reaction around the margins. With Ziehl-Neelsen's stain lesions were seen to contain acid-fast bacilli. The picture was that of an atypical miliary tuberculosis.

COMMENT

There are several features of unusual interest in this case. Aplasia of the bone marrow was caused by an overwhelming toxaemia with a very low resistance. The absence of chest symptoms and minimal radiological findings are very difficult to explain in a case of generalized miliary tuberculosis. The primary focus was probably extrapulmonary. The gross splenomegaly was due to numerous tubercles and there was no evidence of splenic panhaematopenia. The miliary tuberculosis was not seriously considered in the differential diagnosis. Aleukaemic leukaemia was excluded by the marrow findings.

Septicaemia due to an anaerobic organism was the tentative diagnosis.

My thanks are due to Professor J. H. Biggart for his report on the histological section of the spleen, to Dr. M. G. Nelson for the report on the marrow smears, to Dr. C. R. Murdock for the report on the blood, and to Dr. H. B. McDowell for the report on the radiographs.

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Treatment of Typhoid Carrier with Penicillin and Sulphamerazine

The successful treatment of a typhoid carrier, who had resisted combined sulphonamide–penicillin and caronamide, and choramphenicol, was eventually achieved by sulphamerazine and penicillin in dosage similar to that employed in our earlier case (Rumball and Moore, 1949).

CASE REPORT

A boy aged 9 contracted typhoid fever in Egypt in July, 1948, and came under our care six months later as a chronic persistent and profuse faecal carrier. His agglutinations were: typhoid O, 1 in 20; typhoid H, 1 in 250; and typhoid Vi, 1 in 10 standard agglutination and 1 in 20 partial agglutination. *In vitro* sensitivity tests showed: sulphathiazole—insensitive at 25 mg. per 100 ml., sensitive at 50 mg.; penicillin—insensitive at 1 unit per ml., sensitive at 5 units; sulphathiazole and penicillin combined—no demonstrable increase in sensitivity.

Over a period of nine days beginning on February 12, 1949, 19,000,000 units of crystalline penicillin, 75 g. of caronamide, and 39.75 g. of sulphatriad were given. Serum penicillin assay showed a range of 0.08 to 0.3 unit per ml., and sulphonamide concentration from 9.2 to 18 mg. per 100 ml., these levels being obtained immediately before the four-hourly doses of the combined drugs. A scanty growth of *Salmonella typhi* continued throughout treatment, but a profuse growth returned within a few days afterwards, even though the patient's serum on February 18 had inhibited the isolated organism.

Chloramphenicol was considered as a second method of treatment, based on the findings of Smadel *et al.* (1948), Woodward *et al.* (1948), and Murgatroyd (1949) that this drug was active in the acute disease, though at the time no literature was available regarding its effectiveness against the carrier state. The isolated organism was found to be extremely sensitive *in vitro* to chloramphenicol at a dilution of 2.5 mg. per ml. A course of treatment, using 0.25 g. of chloramphenicol four-hourly for seven days, to a total of 10.5 g., was therefore given from April 12 to 18. This dosage, equivalent to 10 mg. per kg. body weight, was based on half the adult dose given in acute cases. Positive stool cultures were obtained consistently during and after this course. A further course, using a threefold increase in dose to a total of 32.25 g., was given from April 25 to May 2, and was also unsuccessful. During the latter course serum sensitivity levels from 0.02 to 0.04 mg. of chloramphenicol per ml. were obtained, and faeces were negative. Apparently inhibition of the organism occurred while there was a high concentration of the drug in the bowel, but with the cessation of treatment the organism reappeared in profusion. In view of the outbreak of typhoid fever in Crowthorne, Berkshire, at the time (April, 1949) the unsuccessful use of the drug in this particular carrier was regarded as an important though disappointing clinical result.

Finally a 10-day course of 29.5 g. of sulphamerazine and 32,200,000 units of penicillin, comparable to that successful in our earlier case, was given in May, during which serum penicillin levels rose to 1 unit per ml., sulphamerazine concentration ranged from 15.8 to 36 mg. per 100 ml., and the patient's serum inhibited the organism in dilutions of 1 in 16. Faeces became negative early in this course of treatment and have remained negative consistently throughout the nine months' follow-up. The Vi titre had also returned to negative. Cure is therefore presumed probable.

COMMENT

It is stressed that cure of a second case with this method warrants no special claim being made of its superior value over other reported successful methods of treatment, but this case again serves to impress the fact that high and sustained blood levels are essential for success. In this case repeated failure with other methods, and success with the third course of treatment, may also be explained on the findings of Fry *et al.* (1948) that intermittent courses of treatment may be more successful than a continuous attack. The advent of chloramphenicol has considerably reduced the clinical complications and hastened recovery in acute cases of typhoid, in which the organism is more accessible to its action, but the treatment of the carrier state is a very different problem. Before abandoning hope in the treatment of carriers it is considered that the combined use of penicillin and sulphamerazine is worth a trial.

Since submitting this article a chronic urinary and faecal carrier of *Salmonella kottbus* has come under our care. Treatment similar to that detailed above was successful. *Salm. kottbus* belongs to the food-poisoning group of organisms. A summary of the case history is appended.

A 21-year-old aircraft hand was notified to us from a military hospital, to which he was admitted in December, 1949, suffering from diarrhoea and vomiting. His stools and urine gave a pure growth of *Salm. kottbus*. He was transferred to our care on January 31, 1950, symptomless and well. The organism was isolated and found to be sensitive to chloramphenicol, and a course of 25 g. was given. Subsequent cultures showed that the urinary infection had been eradicated, but the bowel infection persisted. At the end of February he was given a seven-day course of penicillin, 400,000 units four-hourly, night and day, together with a course of 27 g. of sulphamerazine. On completion of this the faeces were free from *Salm. kottbus*. He has remained under bacteriological surveillance, and during the three months since completing treatment both stools and urine remain free from *Salm. kottbus* infection. This case demonstrates the susceptibility of urinary infection to chloramphenicol and the resistance of bowel infection, which, however, responded to combined sulphamerazine and penicillin.

Our thanks are due to Air Marshal Sir P. C. Livingston, Director-General of Medical Services, for permission to publish these cases, and to Air Vice-Marshal T. C. Morton, consultant in pathology and tropical medicine, for advice and assistance in the bacteriology of the cases.

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The British Standards Institution has issued a draft British Standard for linen textiles for use by local authorities and hospitals. The draft is being circulated to interested organizations so that they may comment on it before August 15. It is based on proposals made by the Local Authority Standards Advisory Committee in collaboration with the Hospital Equipment Standards Advisory Committee.

Reviews

UROLOGY

Essentials of Urology. By J. C. Ainsworth-Davis, M.A., M.D., B.Ch.(Cantab), F.R.C.S., F.R.C.S.Ed. (Pp. 734; illustrated. £2 10s.) Oxford: Blackwell Scientific Publications.

Urology has established itself now as a specialty, and many new textbooks are being published. Some are written by single authors and others by teams of contributors. One misses in the composite works what may be called the personal touch. While they are excellent books of reference, they do not reveal so clearly, as does a book by a single writer, which of the various alternatives described is likely to be the best method of treatment in a given case. Mr. Ainsworth-Davis does not derive sufficient profit from this advantage enjoyed by the single author. He gives an excellent description of the various alternative operations that may be carried out, but he keeps too far in the background and does not tell us enough of his own personal experience of them. Otherwise his book is to be highly recommended. The text is concise and clear, the accounts of after-treatment are excellent, and the diagrams and plates of an exceptionally high order. The general surgeon and postgraduate student could not have a better account of urology than what this book gives them. It is to be hoped that in a second edition the author will be a little less modest and let us know more of his own experience of the operations he so clearly describes.

KENNETH WALKER.

PRINCIPLES OF INDUSTRIAL HEALTH

Industrial Health. By R. Passmore, M.A., D.M., F.R.S.Ed., and Catherine N. Swanston, M.R.C.S., L.R.C.P., D.P.H., D.I.H. Foreword by Professor F. A. E. Crew, F.R.S. (Pp. 110. 4s. 6d.) Edinburgh: E. and S. Livingstone. 1950.

This book is labelled an introduction for students. It is far more. It is a concise, readable—if elementary—account of the principles of industrial health. The writers have drawn on their practical experience in presenting their material, and doctors and industrial nurses, managers and foremen, could all find valuable information here.

After describing the distribution of the working population in this country and the special occupational problems of young and old, the writers discuss methods of assessing the health of working communities. A good short account of the main factors in the physical environment follows. Despite the steady improvement over many years in physical working conditions, it is pointed out that improvement in psychological and social environment has not kept pace, and that in consequence "many are working at three-quarters pressure only." The writers discuss these psychological and social factors and their effect on working efficiency. Chapters on industrial accidents and occupational diseases are included. They are sound, except for the account of the pneumoconioses, which is somewhat muddled and may confuse the reader. Short chapters follow on legislation and on the responsibility of management for health in industry, and the functions in this field of such industrial experts as the personnel manager, the safety officer, and other technical staff.

More and more are doctors being asked to undertake duties in factories and among working groups. If their time is to be used to the full they require some special training. This little book would provide an excellent accompaniment to any short course, and it would alone provide the general practitioner with a useful introduction to medical work in industry.

R. E. LANE.

DRUGS AND TREATMENT

A Concise Applied Pharmacology and Therapeutics. By F. G. Hobart, Ph.C., and G. Melton, M.D., M.R.C.P. With a foreword by Sir Adolphe Abrahams, O.B.E., M.A., M.D., F.R.C.P. Third edition. (Pp. 234. £1 1s.) London: Leonard Hill Ltd. 1949.

The appearance of the third edition of this book indicates that it has been found useful. Since one of its authors is a pharmacist, the publication contains much information required by the practising physician which is not of interest to the student approaching pharmacology in its early stages. The student is then chiefly concerned with understanding the mechanism of the action of drugs and has not yet come to face the practical difficulties of nomenclature, for example. The practising physician, on the other hand, will value a book which begins with a list of proprietary drugs and their definitions or non-proprietary equivalents. For him it is obviously a valuable and handy book of reference.

J. H. BURN.

MARMALADE AND MATERIALISM

A Doctor Digresses. By Kenneth M. Walker, M.A., M.B., B.Ch., F.R.C.S. (Pp. 207. 10s. 6d.) London: Jonathan Cape. 1950.

"If those of you who have brought their Bibles with them will turn to the Book of Leviticus . . ." Thus Kenneth Walker began his 9 a.m. lecture on gonorrhoea twenty-five years ago, and we amiably concluded that the lecturer had wit, style, and an interest in religion. These qualities have remained with him, and in this book he displays them yet again. The book is in truth a series of essays on such subjects as health, the patient, psychosomatic medicine, Western psychology, and Eastern philosophy—a continuing skein through them being skilfully woven by Marmalade, his cat, and Bonnington, an *alter ego* : Marmalade stands for elegance, for grace, and for non-attachment, while Bonnington holds fast to scientific materialism.

Pandit Nehru said recently that the man without internal conflict is a lunatic, and in our author there is a healthy schism between Kenneth, the artist, and Walker, the surgeon, which is scarcely resolved by "K. W.," the well-known medical philosopher. The philosopher tries hard to be eclectic in his approach to authority, but those who have read his other books will know that his heart is with Whitehead against Russell, with Jung against Freud, with Sherrington against Watson, with free will against determinism, with spirit against corpus, with physicians against specialists—in short, with Marmalade against Bonnington. This book adds little to our knowledge of the author's philosophy; but for the interested layman it provides stimulating and even exciting reading, and there are few medical readers who will not find here a new idea well conceived and finely phrased, or an old concept freshly illuminated. If Mr. Walker had given his book an index, it would have been a kindness to reviewers and at the same time have provided a silent testimony to the remarkable range of his

reading and to the extent of his learning. Now and again, however, he is uncritical in his acceptance of authority, as when he fails to examine the statement that nine out of ten of the persons attending the Peckham Health Centre were in a state of ill-health.

He tells us that this book rose phoenix-like from the ashes of a burnt manuscript, an ambitious work entitled "The Philosophy of Medicine." As he watched the flames destroy the result of a year's labour he consoled himself with the reflection that the philosophic method had no place in medicine, which required only careful observation and experiment. This is Walker writing, for nothing is more apparent in the practice of medicine to-day than that it lacks a coherent philosophy. "K. W." should try again.

D. V. HUBBLE.

FANCY FREE

Adaptation. Edited by John Romano, M.D. (Pp. 113. 16s.) Ithaca, New York: Cornell University Press. London: Geoffrey Cumberlege. 1949.

This volume consists of the papers read at the "Dedicatory Program" of the psychiatric unit at the Rochester School of Medicine and Dentistry. A brief editorial introduction is followed by five variations on themes suggested by the title. They are composed respectively by distinguished professors of zoology, physiology, psychobiology, psychiatry, and anthropology, the theme of "adaptation" being chosen on the grounds that it was a concept "central" to them all.

It is impossible to summarize the contents, since the contributors have let their fancy roam with fluent zest. The action of enzymes, the work of Pavlov and Sherrington, the views of sundry philosophers, the behaviour of wild rats and of neurotic goats, the result of a Gallup Poll (published in the *Ladies' Home Journal*) on the belief in the existence of God, the revelations of Freud, and many other matters—all find a place.

It is as if each professor had been set a question in some nightmare examination, "Write down what you know and interests you in not more than 22 pages"; but none complain, and only one seems to ask rather plaintively what it is all about. And who would not be puzzled, for example, about whether it is remarkable or only to be expected that elephants should have legs thick enough to support their weight? If they hadn't—but that is too easy: the elephant—and what else?—does not arise, or falls flat.

DESMOND CURRAN.

In *Energy and Matter* (Staples Press, 10s. 6d.) Dr. R. L. Worrall endeavours to give in a short space an account in simple language of the development of modern physics. He begins with a rapid review of the rise of physical science from the days of Aristotle to the present time. Such a review must of necessity be limited to the main positions taken up by the great physicists upon whose discoveries progress is dependent, and the author has wisely expressed their views in terms used by the discoverers themselves. Even if this method involves a certain degree of discontinuity, it provides a series of solid foundations the veracity of which can scarcely be questioned. Whether the reader who is not already familiar with the conceptions of modern physics will be able to grasp their meaning is an open question, but at least he will have the opportunity of a rapid review of the problems. The author has evidently read very widely, and it is a remarkable achievement to have compressed so much in so short a space. The absence of mathematical terms and symbols will certainly be appreciated by the readers for whom the book is intended.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Divine Healing: What the Bible Miracles Teach. By P. Raymond, M.B., B.S. (Pp. 55. 2s. 3d.) Dorchester: Longmans. 1950.

Illustrations of Anatomy for Nurses. By E. B. Jamieson, M.D. 3rd ed. (Pp. 86. No price.) Edinburgh: Livingstone. 1950.

Manson's Tropical Diseases. Edited by Sir Philip H. Manson-Bahr, C.M.G., D.S.O., M.A., M.D., D.T.M.&H., F.R.C.P. 13th ed. (Pp. 1,136. 45s.) London: Cassell 1950.

Eye Surgery. By H. B. Stallard, M.B.E., M.A., M.D., F.R.C.S. 2nd ed. (Pp. 667. 52s. 6d.) London: Simpkin Marshall. Bristol: John Wright. 1950.

A Textbook of Venereal Diseases. By R. R. Willcox, M.B., B.S. (Pp. 439. 32s. 6d.) London: William Heinemann. 1950.

Regional Dermatologic Diagnosis. By E. Epstein, M.D. (Pp. 328. 42s.) London: Henry Kimpton. 1950.

A Short Textbook of Surgery. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.Ed. 5th ed. (Pp. 676. 30s.) London: Churchill. 1950.

Physiological Mechanisms in Animal Behaviour. Symposia of the Society for Experimental Biology. No. 4. (Pp. 482. 35s.) Cambridge: University Press. 1950.

The Abnormal Pneumoencephalogram. By L. M. Davidoff, M.D., and B. S. Epstein, M.D. (Pp. 506. 105s.) London: Henry Kimpton. 1950.

Living Anatomy. By R. D. Lockhart, M.D., Ch.M. 2nd ed. (Pp. 71. 12s. 6d.) London: Faber and Faber. 1950.

The Effects of Temperature, Humidity, Air Movement, and Solar Radiation on the Behaviour and Physiology of Cattle and Other Farm Animals. By J. D. Findlay, B.Sc., Ph.D. (Pp. 178. No price.) Kirkhill, Ayr: The Hannah Dairy Research Institute. 1950.

The Centennial of the Sheffield Scientific School. By E. O. Lawrence and others. Edited by G. A. Baitsell. (Pp. 206. 20s.) London: Geoffrey Cumberlege. 1950.

The Closed Treatment of Common Fractures. By J. Charnley, B.Sc., M.B., F.R.C.S. (Pp. 190. 35s.) Edinburgh: E. and S. Livingstone. 1950.

Modern Trends in Obstetrics and Gynaecology. Edited by K. Bowes, M.D., M.S., F.R.C.S. (Pp. 778. 60s.) London: Butterworth. 1950.

Supervoltage Roentgentherapy. By F. Buschke, M.D., and others. (Pp. 297. 77s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

Living by Zen. By D. T. Suzuki, D.Litt. (Pp. 187. 15s.) London. Rider. 1950.

Recent Advances in Ocular Prosthesis. By J. H. Prince, F.B.O.A., F.S.M.C., F.R.M.S., F.Z.S. (Pp. 155. 20s.) Edinburgh: Livingstone. 1950.

Emergencies in Medical Practice. Edited by C. A. Birch, M.D., F.R.C.P. 2nd ed. (Pp. 564. 27s 6d.) Edinburgh: Livingstone. 1950.

Irish Medical Directory and Hospital Year Book, 1950. 11th ed. (Pp. 269. 15s. 6d.) Dublin: Parkside Press. 1950.

The Chemistry of Industrial Toxicology. By H. B. Elkins, Ph.D. (Pp. 406. 44s.) New York: John Wiley. London: Chapman and Hall. 1950.

Lipidoses: Diseases of the Cellular Lipid Metabolism. By S. J. Thannhauser, M.D., Ph.D. Edited by H. A. Christian, A.M., M.D., LL.D., Sc.D.Hon., M.A.C.P., Hon.F.R.C.P.Can., D.S.M.(A.M.A.), (Pp. 606. 96s.) New York: Oxford University Press. London: Geoffrey Cumberlege. 1950.

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NON-PULMONARY TUBERCULOSIS

At a time when the incidence of most of the common infectious diseases in Great Britain is declining rapidly, more and more attention is being directed to the continued high mortality from tuberculosis. Unfortunately our knowledge of several factors in the aetiology of this disease is still deficient, and no reliable records are available even for the morbidity rate. Public health interest is centred mainly in pulmonary tuberculosis, and the importance of the non-pulmonary form in causing sickness, deformity, and prolonged invalidity in those who escape death tends to be overlooked. The publication, therefore, of a report[1] to the Medical Research Council on non-pulmonary tuberculosis is to be welcomed, for the committee of experts responsible for planning the investigation, under the chairmanship of Dr. G. S. Wilson, have produced a very informative document. Apart from the intrinsic value of its contents, the report affords an admirable example of what can be achieved by group research. All the investigations were carried out on material obtained in their day-to-day work by hospital pathologists, public health bacteriologists, and tuberculosis officers working according to an agreed plan. The inquiry took its origin at a conference that was called by the Medical Research Council to discuss whether any light could be thrown on the reasons for the increased mortality from tuberculosis during the first two years of the war.[2] The delegates from England, Wales, and Scotland who attended decided to restrict their investigations to non-pulmonary tuberculosis and to organize their work for each country separately. The general plan was for pathologists in hospitals to collect suitable material taken during life or after death and to send it to bacteriologists, working usually in public health laboratories, for determination of the type—human or bovine—of the infecting organism. As soon as this had been done, the tuberculosis officer or medical superintendent was asked to provide information on the patient's occupation, change of address within the preceding five years, number of persons in the home, exposure to contact with tuberculous patients, and the milk supply before and during the war. The report is in two sections, the first concerns England, the second Wales. The inquiries in these two countries were carried out in 1943, 1944, and the first nine months of 1945. It is presumed that the Scottish report will be published later.

In England tubercle bacilli were cultivated from a total of 994 patients; of these, 733 (73.7%) were shown to be infected with the human and 261 (26.3%) with the bovine type. An attempt made to compare the distribution of the human and bovine types according to the age, sex, occupation, address of the patient, and other factors proved difficult for two reasons. First, no figures were available for the true morbidity of non-pulmonary tuberculosis in different parts of the country, so that all conclusions had to be based on the proportions of the two types in different regions; and, since a high bovine–human ratio in one region compared with a low ratio in another might mean either that there was a greater risk of infection with the bovine or a smaller risk of infection with the human type, it was impossible to estimate the real risk of infection with the bovine type in the two regions. Secondly, though the information obtained by the collecting pathologists on the age and sex of the patients and the site of the disease was practically complete, details provided by the tuberculosis officer or medical superintendent about the patients' environment were less satisfactory. Much of the information asked for could not be obtained, partly for reasons connected with the war; and some of it, derived by postal or delegated questionaries, was manifestly so unreliable that it had to be discarded.

Analysis of the figures according to the site of disease showed that the bovine type of bacillus was responsible for approximately 28% of all cases of meningitis, 57% of cases of cervical glandular tuberculosis, 10% of cases of bone and joint disease, and 22% of cases of genito-urinary disease. In all these groups the proportion of bovine-type infections was higher in children than in adults. This was in accord with previous experience: but in contrast with previous experience it was found that the highest proportion of infections with the bovine type was no longer in the 0–4 age group, but in the 5–9 age group. The reason for this change is supposed to be twofold. Owing to the gradual replacement of raw by heat-treated milk for infant feeding during the past 25 years or so the relative risk of infection with the bovine type in the first year or two of life is less than it used to be. On the other hand, the introduction of the milk-in-schools scheme has resulted in a greater relative risk of infection with the bovine type among school-children, many of whom receive milk now who before would have had none at all. Though it is true that most school milk is either heat-treated or comes from T.T. or attested herds, in the early days of the scheme much ordinary raw milk was supplied, and even

[1] *J. Hyg., Camb.*, 1949, **47**, 337.
[2] *Report of the Committee on Tuberculosis in War-time*, Spec. Rep. Ser. med. Res. Coun., Lond., 1942, No. 246. H.M.S.O., London.

at the present time probably about 10% of schools—though a lower percentage of school-children—are still provided with potentially dangerous milk. Further analyses revealed that adult females who developed non-pulmonary tuberculosis were almost twice as liable as adult males to be infected with the bovine type; that 30% of all cases of infection with the bovine type were in persons over 15 years of age; that 87% of patients infected with the bovine type gave a history of drinking raw milk as against 53% of those infected with the human type; and that the lowest proportions of bovine-type infections occurred in the London, North-East, and South-East regions, and the highest in the North-Midland and North-West regions, where tuberculosis in cattle is known to be particularly prevalent. By applying the proportions for the different ages and the two sexes to the recorded deaths from the different forms of non-pulmonary tuberculosis it is calculated that 1,300 persons died in England during the year 1944 from infection of bovine origin.

The investigation in Wales was carried out on a smaller scale. The proportion of infections with the bovine type was found to be lower than in England. Strains of tubercle bacilli were cultured from 112 patients, of which 17%, as compared with the English figure of 26%, proved to belong to the bovine type. How much of this difference is to be attributed to the higher proportion of attested herds in Wales, to the relatively large number of cases of meningitis examined, and to the possibly greater risk of infection with the human type, it is impossible to say. If the figures for England and Wales are combined it may be said that about 24% of all cases of non-pulmonary tuberculosis were due to infection with the bovine type of tubercle bacillus, and that in 1944 approximately 1,350 persons died from non-pulmonary tuberculosis of bovine origin. Previous estimates of this nature have been criticized because they were based on material drawn from selected areas which were not necessarily representative of the country as a whole. No such criticism can be made of the present report. Material was drawn from all parts of the country, and, though not exactly the same proportion of samples from each form of the disease was examined in each region, the authors have, by standardizing the age and sex distribution and by working out alternative arithmetic means, provided figures more reliable than any previously collected. There can be no doubt from their analysis that a large number of deaths, and presumably a still larger number of cases of non-pulmonary tuberculosis, are occurring each year which might be prevented by adequate heat treatment of the milk supply. The Government now have the power of compulsory pasteurization; it is to be hoped that they will soon use it.

FOETAL PATHOLOGY

The pathology of the foetus is a relatively unexplored subject, though as long ago as 1892 Ballantyne, of Edinburgh,[1] made what now appears a notable beginning to the solution of some of its problems with his book *The Diseases and Deformities of the Foetus*, which he styled "an attempt towards a system of antenatal pathology." The foetus, Ballantyne showed, is by no means exempt from the ordinary diseases of adult life, though its response to any particular stimulus may be very different from the more familiar happenings in the adult. But, in addition, the foetus has its own diseases, though for obvious reasons the pathologist has little opportunity to study these in the post-mortem room. Outstanding among these specifically foetal conditions are the "malformations"—the end-results of abnormal developmental processes. In recent years advances in embryology have greatly aided the study of these conditions. Descriptive embryology has provided the "time-table" of normal embryonic development, thus helping to define the period during which the disturbance responsible for a particular malformation must have occurred. At the same time those working in the field of experimental embryology, using the easily manipulable embryos of amphibia, have demonstrated that many of the spontaneously occurring foetal abnormalities can be caused by simple mechanical interference with the developing embryo. Huxley and de Beer[2] have given an account of experiments of this nature, which of course have not provided evidence about the aetiology of spontaneously occurring developmental abnormalities in the human but have merely illustrated the mechanism which has brought about the final results. Indeed, the importance of environmental causes of human malformations has received little emphasis, and from published surveys[3,4] of the work on this subject it might be concluded that inherent defects—that is, genetic abnormalities—are the cause of nearly all congenital malformations. It is of interest that a minor developmental abnormality — brachydactyly — was the first example of Mendelian inheritance demonstrated to occur in man.

This emphasis on the importance of genetic factors in the causation of developmental abnormalities does not come solely from clinical studies. In 1929 Bagg[5] was able to produce, by subjecting parent mice to *x* rays, a strain of animals with familial malformations, including

[1] *The Diseases and Deformities of the Foetus*, 1892, Edinburgh.
[2] *Elements of Experimental Embryology*, 1934, London.
[3] Macklin, M., *Amer. J. Obstet. Gynec.*, 1936, **32**, 258.
[4] Murphy, D. P., *Congenital Malformations: a study of parental characteristics, with special reference to the reproductive process*, 1940, Philadelphia.
[5] *Amer. J. Anat.*, 1929, **43**, 167.
[6] *Med. J. Aust.*, 1945, **1**, 313.
[7] Swan, C., Tostevin, A. L., and Black, G. H. B., ibid., 1946, **2**, 889.
[8] Warkany, J., and Nelson, R. C., *Anat. Rec.*, 1941, **79**, 83.

clubfoot, syndactylism, hypodactylism, and congenital "amputation," all presumably due to induced genetic mutations. However, the association of developmental abnormalities—such as cataract, cardiac septal defects, patent ductus arteriosus, deaf mutism, and microcephaly—with epidemics of German measles, noted in Australia by Gregg[6] in 1941 and later clearly attributed to maternal infection in the early months of pregnancy,[7] demonstrates clearly enough that genetic factors cannot always be invoked as the cause of such abnormalities. Other environmental factors, too, such as deficient diets, have been found experimentally to cause developmental abnormalities, and the relative aetiological importance of heredity and environment therefore still remains to be determined. Experimental work in this field is full of interest and should be rewarding, for from the study of the factors, inherent or environmental, which cause malformations in the human some information may be obtained about why such factors should affect the particular tissues concerned. Hitherto the difficulty has been to find a precise agent with which to influence the developing embryo. But in the chick embryo at least this difficulty has been overcome, and in an interesting paper appearing elsewhere in this issue Mr. P. K. Duraiswami describes how the injection of insulin into the yolks of developing hens' eggs gives rise to a number of developmental abnormalities, including spina bifida, abnormalities of limbs and beak, eye changes, and certain skeletal defects which can be compared to osteogenesis imperfecta.

Limb changes resembling those noted by Duraiswami have been described in the offspring of rats reared on a diet deficient in riboflavin,[8] and it is interesting that he found the administration of nicotinamide and riboflavin largely prevented the abnormal development. From the clinical standpoint it is clear that a number of bone defects are "developmental." While there is good evidence that genetic factors are concerned in the causation of a few of these—such as osteogenesis imperfecta, osteopetrosis, multiple exostoses, and achondroplasia—there are many others whose aetiology is unknown. It is significant, therefore, that bone appears as the outstandingly susceptible tissue in these examples of experimentally induced abnormalities, and that such "physiological" factors as blood sugar, hormones, and vitamins appear to control the normal development of this tissue. Without fuller information it is not possible to judge how closely the condition of the bones in Mr. Duraiswami's experimental animals resembles human oesteogenesis imperfecta, or to suggest how the mechanism of calcification is so grossly disturbed, but it is quite certain that the study of these and other experimentally induced developmental abnormalities of the skeleton is important.

PERNICIOUS ANAEMIA AND GASTRIC CARCINOMA

In the last five years much evidence has been brought forward to suggest that carcinoma of the stomach is a complication of pernicious anaemia. Bourne[1] examined 15 unselected cases and found symptomless carcinoma in three. Wilkinson[2] reported on the causes of death in the 301 patients who died out of the 1,480 patients with pernicious anaemia which he had treated since 1929. He found that 70 died of cancer and that of these the site of the growth was in the stomach in 28. It is impressive that the proportion of cancers which were located in the stomach was twice as high as that which occurs generally, but it is not possible to determine from the evidence whether the unexpectedly large figure was due to an abnormally high incidence of gastric cancer or to a low incidence of other forms. Drs. Johannes Mosbech and Aage Videbaek, in Copenhagen, now demonstrate in a paper published in this issue that carcinoma of the stomach does in fact develop in patients with pernicious anaemia about three times as often as in other subjects. Their series consists of 301 patients. It is not large, but all the patients have been followed up—the longest for 21 years—and 115 deaths have been observed. Results of treatment were so successful that only three deaths could be directly attributed to pernicious anaemia; and the actual number of deaths attributed to other diseases was slightly less than would be expected in the same number of normal inhabitants of Copenhagen (in a group of appropriate age and sex composition) observed for the same number of years. The only exception to this good prognosis was the increased risk of developing carcinoma of the stomach: 15 cases occurred, significantly higher than the expected 5.

Now that the risk is recognized, the important question is how the knowledge can be used to the advantage of patients with pernicious anaemia. Diagnosis must be early if there is to be any chance of treating gastric cancer successfully, and the advisability of regular and frequent barium-meal examinations must be considered. It is, however, doubtful whether many investigations are justified. Jennings[3] has pointed out that the annual risk of a man in his fifties developing gastric cancer is 1 in 1,000, and, even if the risk in a selected group were twice or three times that figure, routine barium-meal examinations would bring few cases to light. It would, of course, be a different matter if a group could be defined in which the annual risk was as high as 1 or 2%: Jennings has suggested that patients with pernicious anaemia might constitute such a group in the first few years following diagnosis, but Mosbech and Videbaek's data do not support his hypothesis. On the contrary, in their series the risk was practically constant at all stages after diagnosis. Why the two diseases are associated is not known. Pernicious anaemia is constantly, and gastric carcinoma is frequently, associated with atrophy of the gastric mucosa, and it is tempting to ascribe the carcinoma to the atrophy. Torgersen[4] has claimed to find evidence for this, in that the growths associated with pernicious anaemia have mostly been

[1] *British Medical Journal*, 1948, 1, 92.
[2] *Lancet*, 1949, 1, 249, 291, and 336.
[3] Ibid., 1949, 1, 457.
[4] *Acta radiol., Stockh.*, 1944, 25, 845.

located near the fundus of the stomach, in the area mainly affected by the mucosal atrophy of pernicious anaemia. Mosbech and Videbaek found the contrary, and they also reached a different conclusion from a review of the literature. In their experience the commonest site for gastric carcinoma was the pyloric antrum, both in patients with pernicious anaemia and in all others. It would therefore seem that mucosal atrophy is not in itself a sufficient explanation, and that the reason for the association must be sought in the disturbed physiology which underlies the development of pernicious anaemia.

THE PRE-THROMBOTIC STATE

Although thrombosis and embolism occur in relatively few patients after operations these complications may be crippling or fatal, and methods for the prevention and treatment of thrombo-embolic disease have been extensively studied. Many of the treatments suggested, such as the use of anticoagulant drugs and ligation of the femoral veins or inferior vena cava, are potentially dangerous and cannot be applied indiscriminately. The selection of patients for treatment is therefore important, and many workers have attempted to find tests to diagnose a "pre-thrombotic state" and to distinguish those patients in whom intravascular thrombosis may occur. All of these tests presuppose that some alteration in the coagulability of the blood is an important factor in thrombosis. This assumption is reasonable, because changes in the blood which might facilitate coagulation are commonly found in patients after operation.[1-4] In 1940 Bergquist[5] suggested that the whole-blood clotting time was shorter than normal in some cases of thrombosis, but in 1945 he reported that the shortening was not constant and the test was, in his view, of no value.[6] Cummine and Lyons[7] reinvestigated the test in 1948, using the capillary tubing method with capillary blood at room temperature. They found that in patients who developed thrombosis the clotting time fell below a critical level of 4–5 minutes just before the onset of thrombosis. In addition they suggested that the fibrinogen in these patients was altered to a form, "fibrinogen B," which was clotted non-specifically by substances other than thrombin, of which naphthoquinone is one. In a series of 550 surgical patients there were 20 in whom the whole-blood clotting time was shortened and the fibrinogen-B test positive. Of these patients, twelve who received no anticoagulant therapy developed thrombosis and eight who had anticoagulant therapy did not develop thrombosis. These findings are clear cut and convincing, but they have not been supported by subsequent work. In 1949 Dunn, Jackson, and Lyons[8] showed that the fibrinogen-B test was positive in many patients who never developed thrombosis, and other workers have found that the capillary clotting time as used by Cummine and Lyons gives variable and unreliable results.[9 10]

A different approach to the problem was followed by Ochsner and his colleagues,[11] who suggest that a decrease in antithrombin combined with an increase in prothrombin may predispose to thrombosis. This combination of pathological findings was found in 30 out of 200 surgical patients. Of these 30 patients 16 developed thrombosis, whereas only one out of the remaining 170 patients showed any evidence of thrombosis. The authors suggest the use of α-tocopherol in the treatment of incipient thrombosis because this substance causes a rise in blood antithrombin. These results are promising, but it will be necessary to await their confirmation before applying them in practice.

1 Wright, H. P., *J. Path. Bact.*, 1942, **54**, 461.
2 de Takáts, G., *Arch. Surg., Chicago*, 1944, **48**, 105.
3 Waugh, T. R., and Ruddick, D. W., *Canad. med. Ass. J.*, 1944, **50**, 547.
4 Brambel, C. E., *Arch. Surg., Chicago*, 1945, **50**, 137.
5 *Acta chir. scand.*, 1940, **83**, 415.
6 Ibid., *Suppl.*, 1945, **92**, 101.
7 *Brit. J. Surg.*, 1948, **35**, 337.
8 *Med. J. Aust.*, 1949, **2**, 266.
9 Greig, G. W. V., *British Medical Journal*, 1949, **2**, 845.
10 Vorhees, A. B., and Pulaski, E. J., *J. Lab. clin. Med.*, 1949, **34**, 1352.
11 Proceedings of the Thirteenth Congress of the International Society of Surgery, 1949, in the press.

EXPROPRIATION OF PRIZE FUND

The National Health Service Act of 1946 gave the Minister of Health power to take over certain hospital endowment funds, and under these provisions he has appropriated the Sanderson-Wells Nurses Prize fund, which was founded by Mr. T. H. Sanderson-Wells, who was for many years honorary surgeon to the Weymouth and District Hospital and is now living in retirement. The securities which formed the endowment were vested in trustees through a trust deed. The annual value of the prize is said to have been about £30. On July 5, 1948, the Minister of Health appropriated the securities at a capital value of about £714. The trustees were not consulted and did not give their consent. The income balance of about £50 standing in the current account was transferred to the Minister through the Bank of England on January 1, 1949. In reply to a Parliamentary question by Sir Ernest Graham-Little, Mr. Bevan stated[1] in October last year that the Sanderson-Wells Nurses Prize fund did not still exist as a separate unit. Mr. Bevan added that he had asked the West Dorset Management Committee to have regard to the objects of the fund in administering the sums received from time to time from the Central Hospital Endowments Fund. Later asked[2] what sum had been allocated from the Central Fund to this prize fund, Mr. Bevan pointed out that the prize fund no longer existed, "and there can therefore be no question of allocation of funds to it." He repeated that the management committee had been asked to bear in mind the objects of the old prize fund, and for the time being they were awarding an annual prize of £5. He had asked them to review the matter in the light of the considerable sums they had received from the Central Fund. As a result of the exertions of Mr. Sanderson-Wells and others an allotment of £19 was subsequently made by the West Dorset Hospital Endowment Committee.

Apart from the fact that the nurses are considerably worse off financially since the Minister appropriated the fund, it is questionable whether he had the right to take it over at all. In Section 7 (10) of the Act the expression "endowment" is defined as "property held by the

1 *Hansard*, October 21, 1949.
2 Ibid., November 3, 1949.
3 *Law Journal*, 1949, **99**, 701.

governing body of the hospital or by trustees solely for the purposes of that hospital." It seems hardly possible that those who framed the Act intended the words "solely for the purposes of that hospital" to cover an endowment made solely for the purpose of a nurses' prize fund. Again, the annual income of the fund is said to be slightly over £25, yet this sum is apparently not being awarded as a prize. Under Section 7 (7) of the Act an obligation is put on the Minister to secure, "so far as is reasonably practicable, that the objects of the endowment and the observance of any conditions attaching thereto . . . are not prejudiced by the provision of this section." The object of this endowment was to provide an annual prize worth about £25–£30, and it would appear to have been prejudiced by the Minister's action, for the sums paid out have been very much smaller, while the value of the securities has probably not depreciated much, if at all.

The Minister is in a very strong position, for in order to challenge Mr. Bevan's actions Mr. Sanderson-Wells or someone else would need to undertake long and expensive litigation in the courts. The Government puts an intolerable burden on private citizens when it passes Acts which are so loosely worded that their provisions appear to be in contradiction to the actions taken under them by a Minister. It would seem to be desirable that cases such as this should be taken to the courts, as the *Law Journal* has suggested,[3] at the expense of the State.

POST-TUBERCULOUS MIDDLE LOBE SYNDROME

An important consequence of tuberculous adenitis may be stenosis of the bronchus of the middle lobe of the right lung. In a review of this relatively common condition Brock[1] has described the occurrence and behaviour of tuberculous lymphadenitis within the lungs and mediastinum. A primary tuberculous focus in the lung is accompanied by enlarged glands at the hilum, which are closely related to the bronchi and may obstruct them or cause ulceration. The middle-lobe bronchus is especially vulnerable, since it and its two branches are long and narrow and are surrounded by glands which drain the middle and the lower lobes. A mass of glands may cause complete bronchial obstruction if it is large or if it occurs in childhood when the bronchi are soft. Such an adenitis may resolve completely, and the effects be only temporary, even if the primary infection occurs in adult life. On the other hand, in the presence of secondary infection bronchiectatic changes will occur and be permanent even when the obstruction subsides. Alternatively, a caseous gland may ulcerate into the bronchus. Its contents, or granulation tissue, may again cause obstruction, or even be coughed up. Caseous tissue often calcifies, and if this happens at a later stage a broncholith or pneumolith will be formed. The contracture caused through healing of the ulcerated bronchus leads to a partial or complete fibrous stricture. Such pathological processes may involve the middle lobe bronchus before it branches or its lateral segment only, and the same changes may take place coincidentally in the cardiac segment of the right lower lobe or the anterior segment of the upper lobe. It is important to recognize these late secondary manifestations as sequelae of tuberculous disease. Each may eventually be complicated by a more or less severe degree of pyogenic infection, and it is usually only when this occurs, which may not be for many years, that the lesion becomes clinically evident. Bronchiectasis is accompanied by pulmonary fibrosis. Fibrosis may also occur beyond a stricture, but distension with mucus or pus is more common, resulting in an abscess or a pyocele. A very severe infection may be associated with the presence of a broncholith. Suppuration may spread to the pleura, other pulmonary lobes, or even more distantly.

This syndrome usually appears in late middle life, the "cancer age," even though the primary lesion occurred in childhood. The sexes are equally susceptible. The symptoms are the result of infection. A pneumonitis may resolve or be followed by an empyema, lung abscess, or by recurrent attacks at the same site. General malaise or unexplained pyrexia may be due to the chronic infection. Cough and sputum suggest bronchiectasis. Haemoptysis is common, and may be repeated and copious, but it is seldom the only symptom. The signs may be very suggestive of bronchial carcinoma. Although a lower-lobe carcinoma may spread to involve the middle-lobe bronchus, and although this bronchus may be compressed by a mediastinal mass of glands, carcinoma of the middle-lobe bronchus itself is very rare. When it does occur it lies peripherally, whereas a post-tuberculous stenosis affects the proximal part of the bronchus : if the exact anatomical location of the lesion is investigated—a lateral radiograph is essential—this diagnostic pitfall will be avoided. Further valuable confirmation of the originally tuberculous cause is afforded by radiological evidence of calcification, either of the primary focus or especially of the gland at the site of the stenosis. Calcification which changes position in successive films indicates a broncholith.

Accurate diagnosis is the first step to treatment. It is clear that radical treatment is often unnecessary, since the disease may remain latent for many years and attacks of inflammation usually subside. In young persons especially surgery is to be avoided, for the tuberculous process may still be active. Operation is necessary if broncholiths or pneumoliths are present, and is indicated if there is a total or subtotal bronchial obstruction ; this can best be demonstrated by bronchography. Excision is the treatment for chronic abscess, but not for bronchiectasis unless there is much purulent sputum. During the operation bronchial occlusion is essential. A middle lobectomy is the manœuvre of choice, but technical difficulties sometimes necessitate removal of the lower lobe as well. Brock operated on 18 of the 60 patients in his series.

[1] *Thorax*, 1950, **5**, 5.

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REFRESHER COURSE FOR GENERAL PRACTITIONERS

SULPHONAMIDE THERAPY

BY

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Indications for Use

The pre-eminent place of sulphonamides in the treatment of many infections has been usurped by penicillin. Their prerogatives indeed are likely to be curtailed still further when the newer antibiotics come into more general use. Nevertheless, they still have a wide application in therapeutics: they are the drugs of choice in meningococcal meningitis, since penicillin passes the blood-brain barrier uncertainly and with difficulty, and in dysenteric and coliform infections, which are unaffected by penicillin; they are almost as effective as penicillin in pneumococcal pneumonia and erysipelas, in which their use is preferable because of their relative cheapness and the convenience of their oral administration; they have been superseded by penicillin in gonococcal and staphylococcal infections and to some extent in streptococcal infections, particularly in septicaemias, except in those cases in which the organism has proved to be penicillin-resistant. When a purulent complication has occurred sulphonamides are ineffective.

The evidence favouring the employment of sulphonamides to prevent the respiratory complications of measles, common colds, and influenza, and for the prophylaxis of the complications of scarlet fever, is in my opinion insufficient to justify their routine use for such purposes. There is considerable statistical evidence that their prophylactic use in daily doses of 0.5 g. for long periods is of value in preventing the recurrences of acute rheumatism, even though sulphonamides are useless in the treatment of the established condition. There seems to be little danger in giving such small doses even for years; nevertheless, further controlled studies must be undertaken before this form of treatment can be recommended in general practice.

Experience gained in the recent war seems to indicate that the use of crystalline sulphonamides and of sulphonamide ointments as topical agents is not very successful in the treatment of infected wounds or in infections of the skin and mucous membranes. Moreover, the prolonged use of sulphonamide creams and ointments often results in severe and intractable forms of sensitization dermatitis. The routine use of sulphonamides as topical agents is therefore to be discouraged, except in the form of eye-drops for the treatment of conjunctivitis, corneal ulcers, and blepharitis, and to prevent infection after injuries to the eye. Even here a mild chronic blepharitis may result from the use of sulphacetamide.

In summary, then, the main indications for sulphonamide therapy to-day are in the treatment of meningococcal, coliform, and dysenteric infections; lobar pneumonia; erysipelas; certain infections of the eye; and in infections due to haemolytic streptococci, gonococci, and staphylococci when these have proved resistant to penicillin.

Absorption, Fate, and Action

When sulphonamides are swallowed they are absorbed to a greater or less extent from the small intestine. Some preparations are completely absorbed, others are hardly absorbed at all. When they are absorbed they become rapidly distributed among all the body fluids, though their concentration in milk is too low to affect a suckling baby. The amino-nitrogen in these compounds is partly acetylated in the body—the degree of acetylation varying according to the preparation used. The acetylated form has no therapeutic effect. A mixture of the free drug and acetyl compound is excreted in high concentration in the urine, but about 30% of the sulphonamide is destroyed in the body.

The concentrations of sulphonamides in the blood (5 to 15 mg. per 100 ml.) which are obtained by therapeutic doses do not kill organisms but inhibit their growth so that they are dealt with by the ordinary defence mechanisms. Their action is due to their inhibiting effect on the metabolism of *p*-aminobenzoic acid, which is required by many species of organism as a growth factor.

Preparations and Choice of Drug

There are numerous official preparations of sulphonamides, many of which are marketed by manufacturers under an astounding variety of names, one of the few undesirable expressions of the inventive genius of the great pharmaceutical firms. The practitioner may well be bewildered by the number of preparations at his disposal and doubtful about which drug to use in any given circumstance and how to use it to the best advantage. Many of the sulphonamides differ only very slightly from one another, and it is more important to know how to use a few properly than to be continually changing to an unfamiliar preparation because of some slight advantage it may be reputed to possess. Actually only three or at most four preparations need be employed; one or possibly two for general infections; one for intestinal infections; and one for application to the eye.

The following are brief notes on the main attributes of the more important sulphonamides.

Sulphanilamide (*B.P.*) is the active principle of the original sulphamidochrysoidin ("prontosil red") introduced by Domagk in 1935. It is rapidly and completely absorbed and quickly excreted. It is relatively soluble so that it does not produce renal complications, though in other respects it is more toxic than the newer sulphonamides and less therapeutically active, having no effect on pneumococcal infections. Its prescription is now seldom indicated.

Sulphapyridine—the famous "M. and B. 693"—has been omitted from the 1948 *British Pharmacopoeia* because of the severe toxic effects it produces, particularly nausea and vomiting. There is nothing it can do that modern sulphonamides cannot do better, and it should never be prescribed nowadays.

Sulphathiazole (*B.P.*) and *Sulphadiazine* (*B.P.*) closely resemble each other. They are both highly active and are rapidly absorbed and excreted, so that they have to be given at short intervals in high dosage to maintain adequate blood concentrations. Both drugs and their acetyl derivatives are relatively insoluble in acid urine. Sulphadiazine is rather less toxic than sulphathiazole, and of the two is probably the preferable drug.

Sulphadimidine ("sulphamezathine") and *Sulphamerazine* (*U.S.P.*) have almost identical qualities. I am prejudiced in favour of the former—possibly on account of its British origins.

Sulphadimidine is more rapidly and completely absorbed than sulphadiazine, so that with equal oral doses sulphadimidine attains a blood concentration approximately twice that of sulphadiazine. It is also more slowly excreted, so that it may be given in smaller amounts and less frequently. The acetylated and free forms of sulphadimidine are more soluble than sulphadiazine in neutral and acid urine, and are thus much less apt to give rise to renal complications, though in other respects the two drugs have approximately the same degree of toxicity. Thus, sulphadimidine is probably the best sulphonamide for routine use, though, as it is possibly a little less active than sulphadiazine, the latter may remain the preferable drug in severe meningococcal meningitis.

Sulphadiazine and sulphadimidine are insufficiently soluble for parenteral administration except in the form of their *sodium salts*. Such solutions are strongly alkaline and should be administered only intravenously. Ampoules containing 1 g. of dry powder are available, and the contents should be dissolved in 10 ml. of normal saline. An excellent alternative is "soluthiazole," which is supplied in rubber-capped bottles ready for use; 5 ml. are equivalent to 1 g. of sulphathiazole. It is a neutral solution and so can be given intramuscularly as well as intravenously—a considerable advantage where babies are concerned. It is seldom necessary to give the drugs parenterally except in very severe infections when it is desirable to obtain rapidly a high concentration of sulphonamide in the blood, or when the patient is comatose and unable to swallow, or when intense vomiting prevents absorption.

Sulphatriad, a combination of sulphathiazole, sulphadiazine, and sulphamerazine, is recommended on the principle that if two or more sulphonamides are administered in combination the therapeutic actions of the different compounds are additive but their solubilities remain independent of each other. Accordingly, it is possible to obtain a high blood concentration without the risk of renal complications. Since we have in sulphadimidine a powerful and relatively soluble sulphonamide it seems superfluous to use sulphatriad, which is also more costly.

Sulphacetamide (*B.P.*) yields a very soluble and almost neutral sodium salt (sulphacetamide sodium *B.P.*) which can be used as eye-drops in concentrations up to 30%.

Sulphaguanidine (*B.P.*), *Succinylsulphathiazole* (*B.P.*), and *Phthalylsulphathiazole*, though soluble in the intestinal contents, are all relatively poorly absorbed, thus permitting them to exert their bacteriostatic action in the intestinal tract. Hence their only use is for intestinal infections, particularly dysenteric infections, and for treatment before and after operations on the colon. All three are non-toxic, but succinylsulphathiazole and phthalylsulphathiazole are absorbed even less than sulphaguanidine and are therefore preferable to it. There is some slight evidence that succinylsulphathiazole is superior to phthalylsulphathiazole in acute dysentery and for the elimination of the carrier state.

From what has been said it would seem that the following four sulphonamides are probably the drugs of choice: sulphadimidine for lobar pneumonia, erysipelas, and coliform infections; sulphadiazine and its sodium salt for meningococcal meningitis; succinylsulphathiazole for intestinal infections; and sodium sulphacetamide for infections of the eye.

Administration and Dosage

Sulphonamides are marketed in tablet form, each of which contains 0.5 g. (7½ gr.). The tablets should be broken into small fragments and swallowed with 2–3 oz. (57–85 ml.) of milk or water. The drugs should be given in full dosage or not at all. The only exception to this rule is in infections of the urinary tract (see below). Full dosage should be maintained till the treatment is stopped. The administration of sulphonamides should seldom be continued for longer than seven days and never for more than ten days. It is always advisable to give an initial "loading dose." Children tolerate the drugs well and require a larger dose than might be expected on a purely weight basis. Over the age of 12 they can be given the full adult dose; between 3 and 12, two-thirds of it; between 1 and 3, one-third; and under 1, one-sixth.

In *lobar pneumonia* and *erysipelas* a "loading dose" of 3 g. of sulphadimidine should be given, followed by 1 g. six-hourly till the temperature has been normal for two or three days.

In *coliform urinary infections*, owing to the fact that sulphonamides are concentrated by the kidneys in their passage from the blood into the urine, it is unnecessary to give the large doses required in other diseases. A "loading dose" of 2 g. of sulphadimidine should be given, followed by 0.5 g. six-hourly.

In *meningococcal infections*, in view of their serious nature, the "loading dose" of sulphonamide should be given intravenously in the form of at least 1 g. of sodium sulphadiazine. The injection should be made slowly. Thereafter 2 g. of sulphadiazine should be given orally followed by 1.5 g. every four hours. Treatment should be terminated only when the cerebrospinal fluid has been sterile for some days and all physical signs are in abeyance. This usually involves the administration of sulphadiazine for seven or eight days. As dehydration is common in cerebrospinal fever, and as there is a real danger of renal complications when sulphadiazine is used under such circumstances, every effort must be made to maintain an adequate fluid intake, if necessary by the use of parenteral fluids. As sulphadiazine is much more soluble in an alkaline medium an attempt must be made to render the urine alkaline by the administration of a mixture containing 20 gr. (1.3 g.) each of potassium citrate and sodium bicarbonate—the frequency of dosage being determined by the reaction of the urine to litmus.

In *acute bacillary dysentery* succinylsulphathiazole can be given in massive doses with complete safety, since little is absorbed into the blood. At least 3 g. should be given four times a day and continued for some days after the stools have become normal. Prolonged treatment, which is perfectly safe with this drug, may be necessary in the eradication of the convalescent and chronic carrier state. The drug has been recommended in idiopathic ulcerative colitis, but in my experience is of little or no value.

In *infections and injuries of the eyes* sulphacetamide sodium is used as eye-drops, though penicillin is more effective in severe infections such as ophthalmia neonatorum. In the treatment of acute conjunctivitis and in the prophylaxis of ocular infections after injuries a few drops of a 10% solution are instilled every two hours. An ointment containing 5% of the drug may be smeared along the roots of the lashes three times a day in the treatment of blepharitis.

Toxic Effects

When modern sulphonamides are properly used toxic effects should be rare, and virtually confined to those few

patients who have become sensitized to the drugs or who have an idiosyncrasy to them.

Some malaise and loss of appetite are not uncommon as the result of sulphonamide therapy, but the distressing vomiting so common after the use of sulphapyridine is seldom produced by the more modern drugs.

A harmless cyanosis due to methaemoglobin was often encountered during treatment with sulphanilamide but is rarely occasioned by the drugs which have been recommended. Very exceptionally, sulphaemoglobinaemia develops, accompanied by cyanosis, shallow respirations, and a rapid pulse of poor quality. I have seen this complication on only one occasion. A slow recovery usually occurs when the drug is withdrawn. Sulphaemoglobinaemia is probably due to absorption of sulphides from the large bowel, and, as this is facilitated by fluid colonic contents, the use of saline purges is inadvisable in conjunction with sulphonamide therapy.

Sensitization phenomena, taking the form of a drug fever with or without a skin rash—usually a widespread rose-red maculo-papular rash which fades on pressure—may occur in a previously sensitized individual after a single dose of sulphonamide or may appear from the fifth day of treatment onwards. In the latter case, when there is only a fever and no rash, it may be difficult to distinguish this toxic manifestation from a recrudescence of the disease. When these sensitization phenomena occur or are suspected it is wise to stop sulphonamide therapy and to change to penicillin or one of the other antibiotics if further treatment is indicated. Sensitization to sulphonamides is common and serious enough to render it highly undesirable to resort to sulphonamide treatment for every minor infection which may occur in practice.

Owing to the low solubility of sulphadiazine and especially of its acetyl derivative the risk of microscopic or gross haematuria and ultimately anuria may be considerable following its use under conditions which reduce the output of urine, such as an inadequate fluid intake, vomiting, diarrhoea, or excessive sweating. These renal complications may be prevented by ensuring a fluid intake of at least five pints (2.8 litres) and preferably six pints (3.4 litres) a day, sufficient to maintain a urinary output of not less than 50 oz. (1.4 litres), and by rendering the urine alkaline. The occurrence of a microscopic haematuria is a warning signal to institute prompt preventive measures. Provided the urinary output is normal the discovery of crystals of the drug in urine which has stood for some time is of no significance. The development of anuria calls for immediate cessation of sulphonamide therapy and for forcing oral and parenteral fluids. If this is not rapidly successful specialist aid should be sought and a trial made of ureteric catheterization. Sulphadimidine practically never gives rise to these renal complications.

Blood dyscrasias are rare after sulphonamide treatment unless it is prolonged beyond ten days, or unless previous sensitization phenomena have been disregarded. They include purpura, haemolytic anaemia, aplastic anaemia, and agranulocytosis. The occurrence of these disorders is an absolute indication to stop treatment.

A few cases of peripheral neuritis have been reported following sulphonamide therapy.

The Nursing Appointments Service of the Ministry of Labour and National Service has been reorganized. One result is that there will be 135 offices of the Ministry instead of 33 where nurses and midwives and would-be nurses and midwives can receive advice about these careers and any help they may want in obtaining posts.

INTERNATIONAL CONGRESS OF RADIOLOGY

MEETING IN LONDON

The Sixth International Congress of Radiology, attended by 2,700 members from 54 countries, was opened by the EARL OF ATHLONE, chancellor of the University of London, on July 24 at the Central Hall, Westminster. Dr. RALSTON PATERSON was invested with the insignia of office as president of the Congress, and gave an address in which he pictured the evolution of radiology from its troglodytic days in beetle-infested basements to its modern status as a mature science helping medicine in diagnosis and treatment. On the evening of the same day British Radiology gave a dinner at the Guildhall to over 600 guests from many countries. The Lord Mayor of London and Vice-Admiral Earl Mountbatten of Burma were the guests of honour, and the latter, in proposing the toast of Radiology, referred to the advanced course in radiological defence and atomic medicine given to civilians and members of the Services at the Royal Naval Medical School at Alverstoke.

The scientific meetings took place in three main groups: (1) General Congress Symposia, four in number; (2) a series of symposia in each of the four main subdivisions of radiology—radiodiagnosis, radiotherapy, radiobiology, and radiophysics; (3) meetings of all four sections, with the addition of electrology, at which more than 300 papers were delivered.

General Congress Symposia

A symposium on supervoltage radiotherapy was held on July 25 at which Dr. R. S. STONE (U.S.A.) evaluated the late effects of the use of radiation in excess of 1,000 kV. There were definite advantages, although the relatively high incidence of deep fibrosis of tissues counselled caution. Dr. O. DAHL (Norway) described the 1,500 kV generator at Bergen, and discussed the factors influencing the choice of voltage and the engineering problems involved. Professor B. W. WINDEYER, the chairman, pointed out that, in the range of one to four million volts, therapy has now emerged from the technically experimental stage and is available for clinical evaluation. Advantages to be derived and problems of organization were discussed.

On the following day Sir STANFORD CADE (London) opened a symposium on radiological achievements (1937–50) with a review of the clinical aspects of radiodiagnosis and radiotherapy, and marked the recent milestones of progress. Dr. EDITH QUIMBY (U.S.A.) pointed out the need for a unified and adequate system of dosimetry for high energy radiations now being developed. She described some instruments designed to meet special problems in this field. Dr. A. LACASSAGNE (France) dealt with the advances in the understanding of the actions of radiation on living tissues, in the physio-chemical mechanism of direct and indirect radiation, and with some aspects of cytoplasmic changes in the cell. Dr. ROSS GOLDING (U.S.A.) reviewed advances in gastro-intestinal radiology, with particular emphasis on the radiology of the small intestine and the use of the Miller–Abbott tube. Gall-bladder radiology had been improved by the introduction of a new opaque medium. Dr. P. FARINAS (Cuba) also discussed opaque media, while Dr. K. LINDBLOM (Sweden) considered the use of water-soluble iodine compounds in the study of trauma to joint-cartilages and other structures. Dr. J. LAWRENCE (U.S.A.) outlined the present status of treatment with radioisotopes of iodine and phosphorus. Dr. RALSTON PATERSON (Manchester) dealt with advances in clinical radiotherapy (1937–50).

Mass radiology of the chest was discussed on July 27. Professor M. DE ABREU (Brazil) traced the development of his work from the earliest attempt at fluorography in 1923 to the final methods presented in 1936. Problems relating to the efficient employment of 180 units operating in Brazil were discussed. He gave some details of the chest diagnostic service which works alongside the mass survey for the further assessment of abnormal shadows. He touched upon the social implications of mass radiology. Dr. A. C. CHRISTIE (U.S.A.), who is ill and whose paper was read by Dr. Orndoff, outlined the development of mass radiology in U.S.A.; it was first applied on a large scale to the examination of the U.S.

Army and Navy, when 15 million recruits were seen during five years, 1940–5. Dr. A. NELSON (Sweden) surveyed the progress in technical developments of mass radiography, especially improvements in brilliance of screens, the employment of mirrors instead of lenses, and the use of automatic exposure timers to ensure uniformity of image density. Dr. P. KERLEY (London) compared the present position of mass miniature radiography with that of B.C.G. inoculation. There were not yet figures to prove that mass radiography on a national scale was justified, although the statistics for selected groups showed the method to be of value.

On July 28 radiation hazards were discussed. Professor ROBLEY EVANS (U.S.A.) presented the quantitative aspects of chronic radium and mesothorium poisoning in a series of 24 men exposed for many years to luminous paint. New methods of *in vivo* estimation of these elements have been devised. Studies are still proceeding, but it appears that the figure of 0.1 μg. of radium as a maximum permissible dose may have a much larger safety factor than was once supposed. Dr. A. BRUES and Dr. S. WARREN (U.S.A.) considered various types of radiation hazards and their control. Professor W. V. MAYNEORD (London) described some of the hazards associated with the use of radioactive isotopes and high energy sources of radiation, such as the 30 meV synchrotron in clinical practice, with methods of controlling them.

Radiodiagnosis

At a symposium on angiocardiography papers ranged over technique and clinical applications, a notable contribution being by Dr. C. WEGELIUS and Dr. J. LYND (Finland) describing apparatus for taking serial radiographs at speeds of up to 12 per second synchronously in two planes, with concurrent electrocardiograms. The films illustrated were impressive for their clarity and degree of contrast. Dr. G. JONSSON (Sweden) stressed the value of selective visualization of the abnormal area and described his method of passing a catheter directly into the aorta. Dr. R. N. COOLEY (U.S.A.) and Dr. T. HILLS discussed the technical requirements in the visualization of congenital defects causing cyanosis, and features of practical importance in the selection of patients for surgical treatment were emphasized.

In a discussion on the small intestine Dr. E. A. ZIMMER (Switzerland) described a contrast preparation which tended to excite slight motor activity and thus gave a more rapid transit through the small bowel, so that it could be examined in one hour; the illustration showed a very satisfactory delineation of the mucosal folds in all its parts. In discussing the significance of meteorism Dr. K. ANDERSON (Denmark) gave his reasons for regarding the interchange of gases between bowel and blood stream as proceeding by diffusion. Tests showed that in mechanical ileus gas accumulated proximally to the obstruction and was mainly due to swallowed air. In a closed loop gas formation does not occur. Dr. FRIMANN-DAHL (Norway) dealt with the early diagnosis of strangulation. Strangulation often excites little output of fluid, and few levels are visible on the plain film. An important diagnostic feature is the presence of a tumour-like opacity due to the matted and incarcerated coils. Dr. F. R. BERRIDGE described changes in the small bowel in subjects suffering from calorie deficiency. Delay in transit, with widening of intestinal calibre and loss of mucosal pattern, were noted, with segmentation of the barium column as seen in the sprue syndrome. The small intestine enema by direct intubation was described by Dr. A. LURAO (Italy), and Professor R. PREVOT (Germany) dealt with the diagnosis of inflammatory conditions.

Under the heading of arthrography the value of the injection of water-soluble contrast media into the joint was discussed by Dr. K. LINDBLOM (Sweden) with reference to the menisci of the knee-joint, by Dr. C. H. NELSON as applied to the shoulder-joints, and by Dr. F. NORGAARD (Denmark) in the diagnosis of lesions of the temporo-mandibular joints. Dr. P. HAUCH (Canada) compared the value of injected oxygen as against "diodrast" or vacuolization in the diagnosis of knee-joint derangements. Professor A. LEB (Austria) showed angiograms of the vessels around joints in rheumatoid arthritis, and demonstrated narrowing of the small vessels and stasis in the veins.

Bone changes in the leukaemias of children were discussed by Dr. J. A. SOTO (Uruguay). Dr. L. DREY (Israel) presented a case of Cooley's anaemia having widespread skeletal changes. Drs. LEFEBVRE, J. LERIQUE, and P. BERTRAND (France) presented a large number of examples of leukaemic bone changes, and Dr. U. COCCHI (Switzerland) dealt with the osseous lesion of lymphosarcoma, myelomatosis, and osteomyelosclerosis.

Radiotherapy

Contributions to a symposium on the presentation of results in the treatment of cancer came from Professor J. HEYMAN (Sweden), Dr. H. F. DORN (U.S.A.), Mr. J. W. BOAG, Dr. P. F. DENOIX (France), Dr. J. CLEMMESON (Denmark), and Professor R. MACWHIRTER. There was general agreement that the present lack of uniformity in methods of presenting results reduced the value of the contributions made by the various workers in cancer therapy. Suggestions for standard methods were put forward by Boag and Denoix. Heyman outlined the more important criteria of cure upon which agreement should be reached. Clemmeson and MacWhirter drew attention to W.H.O. as an appropriate body with which a liaison might be reached, and it was proposed on behalf of the British delegation that an International Committee for standardization of method be set up.

On July 25 the use of radioactive isotopes in therapy was discussed.

Radioiodine (I^{131}) is now emerging from the experimental stage in the treatment of thyrotoxicosis in selected cases, and has proved of value in both primary and metastatic thyroid carcinoma. Radiophosphorus (P^{32}) has proved beneficial in the treatment of polycythaemia vera and in the chronic leukaemias. These points were made in contributions by Mr. G. W. BLOMFIELD, Dr. J. G. HAMILTON (U.S.A.), and Dr. L. O. JACOBSON (U.S.A.). Dr. S. M. SEIDLIN (U.S.A.) gave his experience of cases of metastatic thyroid carcinoma treated with I^{131}, while Professor D. W. SMITHERS remarked that many applications of artificial isotopes, in both treatment and diagnosis, were being tried, but that experience had been short in this country as compared with the U.S.A. He had obtained interesting results in plotting the spread of breast cancer; and in many other fields, such as the rate of absorption of Na^{24} from the bladder, work was in progress.

On July 27 Professor G. E. BERVEN (Sweden) outlined the method used at the Radiumhemmet for treating breast cancer, and gave reasons for the use of pre-operative as well as post-operative irradiation. His figures gave 81.5% five-year cures when no glands were found, and 48.6% five-year cures when glands were involved. He pressed for a committee to standardize rules for presenting results along the lines suggested by Heyman. Professor J. MAISIN and Dr. E. PLUYGRES (Belgium) treated operable cases by radium implant, employing 125–135 mg. of radium for five days. Ten-year survival rates in Steinthals type I and II were 35.8%. Professor M. PONZIO (Italy) reviewed the present position of treatment of cancer of the breast as presented by the literature, and felt that medium tension *x*-ray therapy was still superior to other methods of irradiation. He did not think that there had been any remarkable progress within recent years. Dr. U. V. PORTMAN (U.S.A.) presented a method of classifying types of breast cancer based on clinical and pathological assessment of their extent. Dr. M. LENZ (U.S.A.) made comparison between cases receiving surgical treatment with pre- or post-operative irradiation, and those receiving irradiation only, in various types of breast cancer seen between 1930 and 1942.

In a symposium on radiotherapy of cancer of the larynx Dr. F. BACLESSE (France) described his results in the treatment of cancer of the vestibule, of the glottis, and of the subglottis. He outlined the treatment employed at the Fondation Curie. Mr. V. E. NEGUS dealt with the criteria upon which the employment of surgery, surgery and irradiation, or irradiation alone should rest. Professor A. ZUPRINGER (Switzerland)

considered that satisfactory cure rates were possible by *x* rays, but that tissue reaction in relation to the distribution of dosage was of major importance and still not adequately worked out. He had had promising results when giving the dose in two parts separated by a space of 30 days. Dr. F. E. LEBORGNE (Uruguay) was convinced that *x* rays were in most cases the best form of treatment but advocated the irradiation of minimal areas, not attempting to include lymphatic channels in one treatment. Dr. J. NIELSEN (Denmark) gave statistics for treatment of 115 cases of intralaryngeal cancer. All cases were subjected to fractionated therapy. In cord cases, functional results were excellent. Overall there had been a 57% five-year cure rate.

Radiobiology

The emphasis in the earlier part of a meeting on histology was upon the cellular reaction to radiation, Dr. S. WARREN (U.S.A.) dealing with the general aspects of biological response, and Dr. G. GRICOUROFF (France) with the problem presented by cells which resist radiation action and retain both their viability and mobility, and consequently their capacity for producing new growth. Dr. GLUCKSMAN described the action of radiation in promoting differentiation and so inducing a process by which some malignant cells can be rendered non-viable, although they are not "immediately" destroyed. This process can be followed by the examination of serial biopsies of tumours under treatment, and has a prognostic value. Dr. PALMIERI (Italy) showed that even after the death of the "organism as a whole" there is a short period during which cells still "react" to radiation. The last paper, by Dr. WEST (U.S.A.), dealt with the systemic enzyme changes induced by radiation therapy of malignant tumours, and this contribution produced a lively discussion.

This subject led on to the following day's symposium on radiation chemistry, which centred chiefly on the problems connected with the formation of active radicals within the substance of, and in the neighbourhood of, living cells. Contributors were Dr. M. BURTON (U.S.A.), Dr. P. BONET-MAURY (France), Dr. F. S. DAINTON, Dr. W. M. DALE, and Dr. W. MINDON (Switzerland).

The effect of irradiation and of chemical agents in the production of chromosome changes and in the induction of mutations was the principal subject of another symposium. Similarities and differences between the chemical and radiological changes were discussed by Dr. C. E. FORD and Dr. C. AUERBACH, while Dr. G. BONNIER (Sweden) attributed to indirect chemical change, caused by irradiation, the discrepancy between calculated values for mutations at zero dose and those found in controls. Work by Dr. T. C. CARTER on whole-body irradiation of mice served mainly to demonstrate that a high spontaneous mutation rate existed. A paper by Dr. A. H. SPARROW and Dr. L. F. NIMS (U.S.A.), which was read by the latter, dealt with the cytochemical approach to the understanding of irradiation effects, and included a discussion of desoxy-pentose nucleic acid concentration and of oxygen tension.

A final discussion reviewed the mode of action of ionizing radiations and the many ways in which biological changes might be induced in living cells, especially with changes in their chemical environment. This was the main theme of the papers of Dr. A. FORSSBERG (Sweden) and of Dr. LATARJET (France), while Dr. L. H. GRAY dealt with the influence of radiation quality on the biological response, both for the single ionization and for the integrated result of many ionizations. Dr. A. HOLLAENDER (U.S.A.) described changes in biological response induced by the association of infra-red (heat), light, and ultrasonics with *x*-ray irradiation. Striking modifications of radiosensitivity were observed, although singly these agents had no effect. Dr. B. RAJEWSKY (Germany) discussed the limitations of the target theory. Dr. J. READ presented results from his work upon the roots of *Vicia faba*, which showed that increase of oxygen tension within the cell markedly increased the biological response to *x*-ray dosage.

Radiophysics

Dr. D. W. FRY described the linear electron accelerator and emphasized its suitability in the production of *x* rays in the 3–20 meV region. Experience gained has been applied to the production of a suitable design of apparatus for therapeutic use. A paper by Dr. C. A. TOBIAS, Dr. H. O. ANGER, and Dr. J. H. LAWRENCE (U.S.A.) described experiments on mice using the 184-in. cyclotron built by E. O. Lawrence and his associates. At 190 meV deuterons had a range of approximately 15 cm. in soft tissues. Their ionization intensity is maximal at about 0.7 cm. before the end of their track, and this is approximately four times that on entry. Heavy dosage is thus possible at depth without skin overdosage. Experiments suggested that a useful therapeutic field existed for these high-speed particles. Dr. J. G. TRUMP (U.S.A.) outlined recent research with electrostatic accelerators in the energy range up to 4 meV.

At a symposium on radiological units the difficulty presented by the inadequacy of the "r" unit when high energy radiations were being used was the theme of most speakers. Professor W. V. MAYNEORD suggested the retention of the "r" unit for energies up to 5 meV, but advocated a unit based upon energy absorbed per unit mass of material for radiations of higher energy. This was in line with the views expressed by Dr. LAURISTON TAYLOR (U.S.A.) and Dr. M. FRILLEY (France). Professor R. SIEVERT (Sweden) was more doubtful of the value of an energy unit, and raised the possibility of utilizing certain phenomena which occurred in a vacuum chamber as a possible starting point in the search for a suitable unit.

Treatment was the subject in this section on July 27, when Dr. S. BRENNER (Sweden) described the activities of the Institute of Radiophysics in Stockholm. Constant check is kept upon the output of tubes in the Radiumhemmet by taking measurements in about 15% of all treatments. Drs. H. E. JOHNS and E. K. DERBY (Canada) described the physical aspects of treatment with *x* rays generated by the 22 meV betatron. Dr. L. F. LAMMERTON pointed out the difficulty of attempts to apply a standard system of dosage measurement to many conditions of treatment. An instrument of recent design was presented which enabled the depth dose within a field of any size or shape to be rapidly estimated. Dr. W. J. MEREDITH discussed problems of dosage estimation when using radium implants, and referred to the value of radiography in this connexion. Dr. F. W. SPIERS dealt with the discontinuities in dosage caused by the presence of bone and air-containing tissues, and described attempts to calculate dosage modifications. Dosage variations within bone were discussed. The effects of heterogeneous tissue were much less in evidence when higher energy ranges were used. Dr. W. C. WILSON gave an account of the development of the physical aspects of teleradium therapy since 1937, and gave some description of apparatus and techniques employed.

A symposium was also held on the production and physical properties of radioisotopes, when the production and distribution of radioisotopes in Oakridge, U.S.A., Chalk River, Canada, and Harwell, Great Britain, were discussed respectively by Dr. P. AEBERSOLD, Dr. A. J. CIPRIANI, and Dr. H. SELIGMAN. Methods of standardization were presented, and the steps taken to safeguard those handling radioactive material were described. Emphasis in the clinical use of isotopes has shifted somewhat from therapeutic to diagnostic applications. Dr. L. D. MARINELLI (U.S.A.) described investigation of the ionization which took place in air around beta-ray emitting sources.

Exhibitions

The largest technical exhibition of *x*-ray plant and equipment ever to be held in Britain filled both of the Royal Horticultural Halls. Manufacturers from many countries were represented. The Science Museum in South Kensington arranged a historical exhibit, including a copy of Roentgen's original description of his discovery in 1895 and a print taken by him of his wife's hand. In the main meeting-place of the Congress at the Central Hall was an impressive display of radiographs and of photographs of machines and apparatus.

Reports on Protection and Radiological Units

During the closing ceremony on July 28, Sir ERNEST ROCK CARLING, chairman of the International Committee on Radiological Protection, read a summary of the committee's report, in which it was recommended that the tolerance dose for workers continuously employed in radiological departments

should be reduced to 0.5 r per week. Dr. LAURISTON TAYLOR, secretary of the International Committee on Radiological Units, in summarizing its report, said that for radiations of higher energies than 5 meV the "r" unit should be replaced by one based upon energy absorbed per unit mass of tissue.

The next Congress will be held in Copenhagen in 1953.

STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS MENINGITIS

Streptomycin trials have been in progress for some time in 25 hospitals, under the guidance of the Medical Research Council, and the Ministry of Health recently held a conference of interested workers to discuss the records of 369 patients with bacteriologically proved meningitis, with or without generalized miliary tuberculosis, who had been under observation for from 10 to 22 months. The Ministry has now issued the following report of their general conclusions.

General Results

There appears to be a belief prevalent amongst medical practitioners that streptomycin treatment does no more than prolong life or produce "recovery" as a physical and mental wreck. This is not true. It seems a better representation of the facts to say that, provided skilful treatment was given *early in the disease*, some 40% of patients made a complete recovery, except in some instances for minor disabilities which at the time of assessment did not interfere with their leading a normal life. Medical practitioners who have doubts about the efficacy of treatment would probably have better impressions if they were to take the opportunity of visiting some of the special units treating these patients and seeing for themselves. They will be welcomed at these units. Before the introduction of streptomycin treatment, proved cases of tuberculous meningitis were inevitably fatal with no indisputable evidence in support of alleged exceptions. In the series under review about 1 patient in 4 survived. More precisely, a mortality of well-nigh 100% was reduced to 71.4%, and to 50.7% for early cases. Of those who survived 31% had normal cerebrospinal fluid and approximately 89% were clinically fit and well. Approximately 40% of the early cases survived and were clinically fit and well. In all, 104 of the 369 patients survived.

The 104 survivors were followed up at the end of a further year, giving observation periods varying from 22 to 33 months. All were still alive. Eighty-eight were clinically fit and well, 59 (57%) had normal C.S.F. Of the 16 not fit and well 6 were under age 4 and described as "mentally retarded"—a condition on which it is perhaps unwise yet to make a definite pronouncement; 2 were suffering from genito-urinary tuberculosis; 8 had been "unfit" at the assessment a year previously and included 3 with bone or joint tuberculosis, 1 with optic atrophy registered as a blind person, 2 paralysed and incontinent, 2 "emotionally unstable," one of them being also deaf.

At the end of 22 months the overall survival percentage was 27 for meningitis alone and 17 for meningitis complicated by generalized miliary tuberculosis. Amongst those patients who were observed for longer periods there was no fall in those percentages. For early cases of meningitis there were 48% of survivors at 16 months and at 2½ years, but for advanced cases only 12% at 13 months and only 10% at 2½ years. This emphasizes the importance of prompt diagnosis and treatment.

Methods of Treatment

Only exceptionally did a patient suffering from meningitis respond satisfactorily to intramuscular treatment alone; that occurrence was even more rare with miliary tuberculosis plus meningitis. Intrathecal treatment accompanying intramuscular treatment gave appreciably poorer results when it was given on 50% or less of the intramuscular treatment days in a given period than it did if given more intensively. The general trend of results within homogeneous clinical groups seems to be towards better chances of survival with more intensive intrathecal courses. This assumes, however, concurrent intramuscular treatment for at least two-thirds of the days in a given period. There is no unequivocal evidence on the optimum level of intensity of intrathecal treatment above 75% of the days in a given period. The best results were obtained in patients with early meningitis. Early diagnosis and prompt treatment are of the first importance.

In patients suffering from miliary tuberculosis without meningitis, examination of the cerebrospinal fluid at the commencement of, and at intervals during, streptomycin treatment is important. One-third of the cases of miliary tuberculosis so treated developed meningitis during treatment, and about one-fifth died following it. Meningitis can develop as late as the seventh month of a course of treatment for miliary tuberculosis, and some workers have reported even later onsets in cases not in the series reviewed. There was no evidence that "prophylactic" intrathecal treatment prevented the occurrence of meningitis in patients during the course of their treatment for miliary tuberculosis, and what little evidence there was seemed to incline in the direction that it did not.

Assessment of Results

There is a good deal of difficulty in comparing the results obtained by different observers owing to differing conceptions of what constitutes a normal cerebrospinal fluid. Accounts given should state clearly what is the definition adopted in terms of cerebrospinal fluid cells, protein, and sugar. In the series under review the reports given by the hospitals were all compared with a severe standard of normality—namely, per ml. of cerebrospinal fluid; cells not more than 4; protein not more than 40 mg.; sugar not less than 45 mg. During the period of observation there was no instance of relapse in a patient whose cerebrospinal fluid had attained to that standard and who was at the same time clinically fit and well. Further investigation is, however, needed into the possibility of relapse after longer periods, to distinguish relapse from reinfection, and the possibility of tuberculous lesions arising later elsewhere in the body.

Although it was stated in general terms that recovered patients were mentally normal, rather backward, etc., there would be great advantage in recording detailed psychometric assessments, and their value would be enhanced if there were appended any information derived from school medical records or other sources about the mental condition prior to the onset of illness. Vestibular function and deafness should also be investigated and recorded in relation to recovered patients.

Laboratory Findings

Bacteriological proof is of the first importance in assessing results. It does not seem to be fully realized that on occasions this may be obtained only after a large series of negatives over a long period before eventually a positive is obtained. The most extreme example in the series was a patient who had 61 negative reports in the course of about 10 months before a positive was obtained in the 62nd. The attempt to obtain bacteriological proof should not be too readily abandoned. The larger the volume of a sample of cerebrospinal fluid it is possible to send to the bacteriologist for examination the greater is the likelihood of his being able to obtain a positive result.

The importance of precise quantitative estimates of the cerebrospinal fluid sugar content as a guide in assessing progress is becoming increasingly recognized. It is less well recognized that, whilst cerebrospinal fluid examinations are necessary at intervals to assess progress, it is also necessary, if there is to be research into the relative efficacy of different treatment regimes, to make cerebrospinal fluid examinations at certain definite stages. These are: before and after proposed dates of commencing and ending treatment, on discharge, in the earlier follow-up examinations, and from time to time in the later ones.

There will always be a proportion of patients for whom it is not possible to secure consent to a post-mortem examination, but for research to be of real value necropsy of 100% of the patients who die should be the aim.

Future Research

Apart from the investigation of results over the extended observation periods now in progress, it is hoped to organize further more intensive investigation by selected hospitals into aspects of streptomycin therapy which the recent analysis either failed to clarify sufficiently or revealed as matters which needed special study. With the general release of streptomycin to all practitioners and hospitals there has been a considerable decline in the number of patients admitted for treatment to the selected hospitals participating in this investigation. In order that research may be carried out on the relative merits of different modes of employment of streptomycin in patients clinically comparable, adequate numbers are needed. The greater the number of patients available the more speedily can an answer be found leading to yet better results and the preservation of useful human lives. It is most necessary therefore to give the selected hospitals the opportunity for admitting these patients if they have accommodation available.

EPSOM COLLEGE

The ninety-seventh annual general meeting of the governors of Epsom College was held at 49, Bedford Square, London, W.C., on July 7, with Dr. Harold Spitta, the chairman of the council, in the chair. The results of the last election of pensioners and foundation scholars were announced by the chairman. Dr. Spitta reported that the progress of the school had continued to be most satisfactory. Rises in costs had forced the council to raise the fees from Michaelmas, 1950, and to make a charge for stationery and the use of books. The council intended to appeal for funds with which to make lasting improvements to the school in commemoration of the centenary of the college and its Royal Medical Foundation. The following eight members of the council were re-elected for a further period of three years: Miss Janet K. Aitken, Sir Ernest Goodhart, Mr. J. W. Horsford Hodgson, Mr. Frederick G. C. Morris, Sir Cosmo Parkinson, Mr. Cyril J. Parton, Dr. Harold Spitta, and Mr. B. N. Wallis, F.R.S. Colonel Norman C. King, Mr. H. H. Rew, and Mr. H. A. Deeker were reappointed auditors for the ensuing year. A cordial vote of thanks was passed to all honorary local secretaries, the British Medical Association and its Charities Committee, numerous panel committees, and the editors of the *British Medical Journal*, the *Lancet*, and the *Medical World*, through whose generosity and help the funds of the college and its Royal Medical Foundation have benefited during the past year.

The Ministry of Health states that the Prison Commission recently approached the Minister of Health about the psychiatric treatment of offenders serving short sentences. Such treatment may be incomplete when the offender is discharged, and if not continued any benefit from it is likely to be lost. But if arrangements could be made for the treatment to be given by a regional hospital board psychiatrist while the offender is in prison it would probably often be possible to continue it after discharge. The Minister does not object to arrangements being made by regional hospital boards and local prisons for consultants to treat prisoners serving short sentences with a view to continuing the treatment if necessary after discharge from prison. Conversely, prison medical officers who have psychiatric qualifications could assist at regional hospital board clinics. The Minister considers this proposal to be an important social service which should be developed where possible, and hopes that any approach made by local prison authorities will be sympathetically considered.

Correspondence

Residual Insecticides in Assam

SIR,—Dr. D. M. Bertram has recorded the results of an inquiry into the relative efficacy of D.D.T. and benzene hexachloride ("gammexane") in the control of *Anopheles minimus* in Assam (May 20, p. 1200). He reached the conclusion that many anophelines landing on walls treated with D.D.T. were stimulated rather than killed, and though the numbers caught in treated houses were materially reduced the anopheline mosquito population able to bite was not materially changed.

My colleague Dr. Alan Gilroy, also working in Assam on *A. minimus*, has asked me to report the following findings, which do not support Dr. Bertram's conclusion. The technique of treatment and checking was as described by Dr. Bertram. D.D.T. was applied at 45 and 90 mg. per sq. ft. (929 sq. cm.), B.H.C. at 10 mg. of the gamma isomer per sq. ft. Dead mosquitoes were counted on floor sheets, and traps containing mosquitoes which had tried to emerge were removed and kept under cool conditions for 24 hours' observation, others being substituted in the huts. Results at one month are summarized below.

Treatment	Mosquitoes Collected			Mosquitoes in Traps Surviving 24 Hours
	Dead on Floor	In Trap		
		Dead	Alive	
(*a*) All mosquitoes:				
B.H.C.	134	144	777	66
D.D.T. 45 mg. ..	13	44	361	47
D.D.T. 90 mg. ..	3	41	245	7
(*b*) Anophelines only:				
B.H.C.	50	59	104	8
D.D.T. 45 mg. ..	5	33	56	2
D.D.T. 90 mg. ..	0	19	37	2

The anophelines included 135 *A. minimus* and 17 *A. leucosphyrus*, none of which survived 24 hours.

The figures show no material survival following contact with D.D.T. in excess of that following contact with B.H.C. Care was taken to prevent contamination of cages, a possible cause of mortality. If it occurred it is not likely to have exceeded the contamination of the cages from huts treated with B.H.C. in which the survival rate is greater than reported by Dr. Bertram.

In my opinion both of these insecticides may be of great value in Assam, and ultimately it might prove desirable to alternate them. It would be regrettable if either of them were to be condemned without very full trial and independent repetition of work to confirm results, such as is now being made in the case of Muirhead Thomson's work on D.D.T. in the control of *A. gambiae* in Africa.—I am, etc.,

London, W.C.1. G. MACDONALD.

Haemorrhage from Peptic Ulcer

SIR,—Your two articles by Drs. C. D. Needham and J. A. McConachie and by Drs. A. G. Ogilvie and I. O. B. Spencer (July 15, pp. 133 and 138) provide further useful data on the mortality from bleeding peptic ulcer and its response to treatment. But the only indication that Drs. Needham and McConachie give of the treatment employed in their cases is that it was the usual routine conservative regime employed in medical wards. But, Sir, may I urge that there is no usual routine? Opinion has been divided between the extremes of those who feed and those who starve their patients, and those who transfuse on the least provocation and those who transfuse only when the late manifestations of exsanguination supervene. May I ask, therefore, Drs. Needham and McConachie to state whether their patients were starved or fed, and if fed when and

on what? May I also ask whether their patients were transfused; if so, on what indications and how much? I ask this, Sir, because I think we still have much to learn about the medical treatment of bleeding ulcer, and we can all learn if we are in full possession of the facts.—I am, etc.,

London, W.2. G. W. PICKERING.

*** The reply of Drs. Needham and McConachie to Professor Pickering's inquiry appears below.—ED., *B.M.J.*

SIR,—We are grateful for this opportunity to reply to Professor G. W. Pickering's letter. We would suggest that for some years past it has not been usual to treat haematemesis by either starvation or full immediate feeding. The "usual routine conservative regime" employed in the Aberdeen Royal Infirmary lay somewhere between those extremes—viz., fluids by mouth from the time of admission (2–5 oz. = 57–142 ml. of half-normal saline or of half-strength milk hourly or two-hourly), going on to thickened feeds the second day, and small amounts of pounded-chicken type of solids on the third day. Minor differences existed between the three medical units concerned, but the most "cautious" and the most "liberal" feeding wards showed the same mortality, which was slightly higher than that in the "intermediate" feeding ward, which, however, seemed to have dealt with a smaller proportion of severe cases. The appended table gives details of the blood transfused.

		Not Transfused	Transfused	
			Number	Average Amount of Blood per Patient Transfused (M.R.C. Bottles)
Fatal ..	Recurrent	3	48	4·9
	Non-recurrent	3	12	
Survived	Recurrent	14	59	4·5
	Non-recurrent	288	49	2·4
Total		308	168	4·08

The indications for giving blood can best be estimated from the numbers transfused and the amount of blood used. There was never any hard-and-fast policy laid down on this point, but blood was not withheld until severe exsanguination was evident.—We are, etc.,

Aberdeen. C. D. NEEDHAM. J. A. MCCONACHIE.

Anaesthesia in Heart Surgery

SIR,—Dr. D. C. Devitt (July 29, p. 295) is of course absolutely correct in stressing the importance of smooth induction of anaesthesia and of adequate oxygenation in patients who are to be the subjects of cardiac surgery. I believe, however, that his objections to the use of thiopentone for this purpose are not necessarily valid.

It may be of interest if I describe briefly the method that I and my colleagues at Guy's Hospital have found useful in anaesthetizing Mr. R. C. Brock's cases of mitral valvulotomy (we were not concerned in Case 6 of the series described in the article published in your issue of June 3). Preliminary medication is with papaveretum ("omnopon") and scopolamine, and the patient sucks an amethocaine tablet for fifteen minutes before coming to the anaesthetic room. The larynx is then anaesthetized with 2% "butyn" or amethocaine, as if for bronchoscopy, and 5% thiopentone is injected very slowly—the slowness being of great importance—until the patient is unconscious and the jaw relaxed. The dose required to produce this effect is not greater than 0.5 g., and is sometimes less than this. The largest possible cuffed endotracheal tube is then passed under direct vision, and anaesthesia continued with ether and oxygen only.

When using this method we have always found induction to be smooth and free from untoward incidents. Provided that the thiopentone is really injected slowly, significant circulatory depression does not seem to occur, and I know of no quicker or more certain way of gaining complete control of the situation.

I agree with Dr. Devitt in his reluctance to use cyclopropane in cases of mitral stenosis, where there is always a considerable element of myocardial insufficiency. I have no such reluctance, however, in the cases of congenital heart disease which I anaesthetize, for in these the heart muscle appears usually to be extraordinarily healthy. The technique of induction in children suffering from these conditions is different from that for adults. Premedication is by pentobarbitone sodium, administered orally, and atropine, and anaesthesia is induced with cyclopropane and ether by means of a facepiece to a sufficient depth for the passage of a tube by direct vision.—I am, etc.,

London, S.E.1. E. H. RINK.

Treatment of Painful Amputation Stumps

SIR,—After reading the article by Drs. W. Ritchie Russell and J. M. K. Spalding (July 8, p. 68) we think it worth while to mention a form of treatment now under trial at Queen Mary's Hospital, Roehampton.

The treatment consists in infiltrating the painful area with a local anaesthetic of prolonged action, in this case "prolongal" benzocaine, which is 2% benzocaine in urethane. This preparation was devised by Dr. Rappaport and was kindly supplied to us by the manufacturers, Messrs. Zori, of Tel Aviv. After injection urethane is absorbed and benzocaine, being insoluble in water, is precipitated in the tissues in the form of tiny crystals. These crystals persist in the tissues for about four to five weeks and are very slowly absorbed. The pain-killing effect, however, in most cases seems to last much longer.

The injection is performed under general anaesthesia, as there is a period of initial pain which we try to avoid, and, furthermore, a psychological effect is also achieved. In most of our cases other forms of treatment have been tried and failed to bring about an improvement.

So far the results have been very encouraging, provided the cases were well selected, and the relief from pain is sometimes quite dramatic. The selection of cases is most important. The pain has to be due to local causes if the treatment is to be successful. No improvement can be expected if the pain is of psychoneurotic origin.

The number of cases treated is still small and the period of observation too short to draw any valid conclusions, but we hope to be able to report further details and results when a larger series of cases has been treated and observed.—We are, etc.,

Queen Mary's (Roehampton) Hospital, London, S.W.15. M. VITALI. J. KOHN.

Treatment by Mechanical Vibration

SIR,—In 1949 I wrote pointing out to you that mechanical vibrations had been used for many years prior to Dr. Ritchie Russell and that they were of value in other painful conditions beside amputation stumps, but that there was a danger to the operator. This last point has been conceded in Dr. Russell's report (July 8, p. 68). It is amusing to find in the book by Dr. James Ross (then assistant physician to the Manchester Royal Infirmary) called *Diseases of the Nervous System*, published by J. and A. Churchill in 1885, a reference to "mechanical vibrations" from which I send a quotation:

"Some years ago Dr. Mortimer Granville was led to try the effects of rapidly tapping the skin over the fifth nerve in a case of fascial neuralgia by means of a Bennet's percussion hammer, using the pleximeter as a shield. The results were so encouraging that he gradually extended the application of mechanical vibrations as a therapeutic remedy to various other nervous diseases. With the view of better regulating the number and strength of the blows which can be delivered in a given time, Dr. Granville had an instrument constructed which he names 'percuteur.' The newest and most efficient is worked by electricity. . . . Dr. Granville believes that by its use he can relieve neuralgia in a considerable number of cases."

—I am, etc.,

Manchester. S. SHUBSACHS.

Crisis in Tuberculosis

SIR,—The recent memorandum on tuberculosis from the Ministry of Health to regional hospital boards and local authorities (July 15, p. 162) will be welcomed by all who strive for the welfare of the consumptive patient. The declaration (though long overdue) that "many more beds must be made available quickly," and that the Minister "deems it necessary to augment the insufficient resources of sanatoria and tuberculosis hospitals by using a proportion of beds in general hospitals for tuberculosis cases," suggests that the tuberculous patient may perhaps eventually receive a fair share of the medical resources of this nation.

Most chest physicians will agree with the recommendation to use beds pre-eminently for recoverable cases, and to expedite the "turn-over" of cases in hospital beds. It is surprising to find that an official document which advocates such formerly heterodox practices as this, as well as the active treatment of tuberculosis cases in their homes, nevertheless clings to the idea of "central oversight of admissions and discharges by headquarters medical staff." Throughout the country to-day waiting-lists are longest where this rigid bureaucratic control is imposed, and the most successful improvisations and bed economy are to be found where each chest physician has his own direct charge of hospital beds, no matter how few.

If indeed beds are to be made available quickly it is of paramount importance that general hospitals shall open their doors not primarily to relieve central waiting-lists but to help the patients in their immediate locality. To allocate direct control of general hospital beds to each local chest physician, both for tuberculosis and non-tuberculous illness, should facilitate the immediate full and proper assessment of each newly diagnosed case. In this way recommendations for admission to major sanatoria would become more selective, and active therapeutics in the home (which must be supported by hospital facilities) would soon become more widely practised. The disrepute of the old "dispensary system" was largely attributable to its lack, in practice, of such proper facilities, though in theory these were often alleged to be available.

The solution of the appalling problem of waiting-lists for sanatoria is not to be found through ponderous central administration but by providing chest physicians with the necessary facilities to do their job properly.—I am, etc.,

Reading. W. H. TATTERSALL.

SIR,—The memorandum of the Ministry of Health on the treatment of tuberculosis, published in the *Journal* (July 15, p. 162), practically endorses most of the timely recommendations of the Scottish Committee in their crisis expansion programme. We all look forward to the provision of the urgently needed beds (plus nurses) in general and in fever hospitals. How many beds there are readily available for the admission of our patients we just don't know, but I feel that these facilities will not be so plentiful, nor will they be placed at our disposal as quickly as they are required. It has been acknowledged by the Scottish Committee as well as by the Minister that something else, and something almost immediately available, has got to be done without further delay. Long before the authorities concerned with, and responsible for, the control of tuberculosis deemed fit to take up the challenge, several enterprising chest physicians followed the lead given by Dr. Toussaint and organized some scheme of active domiciliary treatment.[1-6]

However, a crisis expansion of such an emergency scheme, which at once would make a large number of sanatorium beds quickly available for early and urgent cases, clearly depends on whether the chest physician can carry on collapse treatment at the chest clinic. A considerable proportion of the old dispensaries—though they are now called "chest clinics"—are lacking the equipment and often also the accommodation for *x*-ray examination and collapse treatment. In order to meet the requirements of a modern chest clinic, and to give the chest physician and the young trainee specialist the widest possible chance of diagnostic and therapeutic clinical work outside the chest hospital, I have suggested the introduction of mobile clinics.[7,8] Such a mobile unit, installed in a caravan, could—in a rota service—be operated by one travelling team in conjunction with the existing dispensaries of a suitable area. It is time now, as you put it in your leading article (July 8, p. 92), "that something is done as an emergency operation." The rapid transformation of our obsolete dispensaries—or rather "visiting stations"[9]—into workable chest clinics is one of the most urgent operations if the crisis expansion of the tuberculosis service is to become a reality.—I am, etc.,

Wolsingham, Co. Durham. E. G. W. HOFFSTAEDT.

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Poliomyelitis and Inoculations

SIR,—In view of the recent discussions concerning the relationship between injection and the onset of paralysis in the injected limbs, I should like to give details of a case which was under my care in 1947, during the peak of the poliomyelitis epidemic. At that time I was resident medical officer in charge of medical wards in a general hospital. The patient concerned was a girl of 21 who was sent to me by an outside practitioner with a diagnosis of boils which would not respond to treatment.

On examination the girl had a temperature of 100° F. (37.8° C.) and on her back were four or five subacute boils which were not particularly tender to pressure. Apart from this there were no abnormal physical signs. The patient was kept in bed under observation for two or three days, during which time her temperature rose to 101.5° F. (38.6° C.) in the evenings, and subsided to 99.5° F. (37.5° C.) in the mornings. In view of the fact that the boils did not improve, penicillin therapy was commenced. The patient was given 20,000 units of penicillin intramuscularly every three hours. There was no change in the patient's condition for the next two or three days, and on the fourth day after treatment she complained of pain in both legs. At the time this was thought to be due to the injections. However, on the fifth day the patient discovered that she could not move her legs. On examination a flaccid paralysis was found to be present in both legs. A lumbar puncture was done, (this was typical of poliomyelitis), and the patient was transferred to an isolation hospital. I saw her again three months later and discovered that there was still a severe degree of residual paralysis in both legs.

About this time I read the article in the *British Medical Journal* (March 19, 1949, p. 465) which suggested that the degree of paralysis bore a relationship to the amount of exercise undertaken in the pre-paralytic stage. I observed to myself at the time that in the case of this particular girl, although she had been resting in bed for at least seven or eight days before the onset of paralysis, she had been left with a severe degree of paralysis in both legs after three months.

I thought no more of the case at the time.

During recent weeks on thinking back I realize that in the case of this girl we had been giving intramuscular injections in both thighs and nowhere else, and that in her case it was her two legs that had been affected, and nowhere else. In view of this and similar cases reported I think we should seriously consider whether it is trauma due to the needle passing through the muscular tissues which predisposes the limb to paralysis, this effect being independent of the contents of the syringe.—I am, etc.,

Newport, Mon. J. NEWCOMBE.

Vaccination Certificates

SIR,—It might be well to add to the useful information on vaccination and inoculation certificates in Sir Philip Manson-Bahr's letter (July 22, p. 215) the reminder to doctors advising migrants overseas that, although the official certificate form states, "This certificate is not valid for more than three years from date of issue," several quarantine authorities in the Far East, and possibly elsewhere, strictly limit the validity of certificates against smallpox for their area to 12 months from date

of issue. One authority recently limited the validity to 60 days. These "parochial" regulations seem to be altered with very little notice and are apt to cause very considerable trouble on attempting to disembark.—I am, etc.,

London, E.C.2. O. MARRIOTT.

Folic Acid and Pernicious Anaemia

SIR,—We have read with interest the article by Dr. H. Fuld (July 15, p. 147) entitled "Effect of Vitamin B_{12} on Neuropathy in Pernicious Anaemia Treated with Folic Acid," in which the conclusion is drawn that since neurological lesions or symptoms developed during the course of such treatment there existed a causal factor in the folic acid.

It is, of course, highly desirable that clinical findings of this sort should be brought to the attention of the medical public, and equally desirable that whenever there are differing interpretations these should also be expressed, in order that scientific knowledge may progress through the interchange of critical observations until a truly accurate consensus of opinion is reached. With the desire to be helpful in the clarification of the proper role of folic acid in the treatment of anaemias we wish to cite a few comments and findings which were in all probability not available to Dr. Fuld at the time of the writing of his paper.

An editorial which appeared in the *New England Journal of Medicine* (March 23, 1950) takes the stand that while folic acid does not possess the power of protecting the nervous system against the development of disorders as concomitants of certain macrocytic anaemias, as does liver or vitamin B_{12}, and whereas it does not possess therapeutic properties in respect of these neural lesions, it nevertheless does not play a toxic, causal, or harmful role in this direction. If this is true, then there is every reason to avail ourselves of the benefits of this medication, which has proved its usefulness in eliciting reticulocyte and erythrocyte responses. A proper understanding of its action, however, would call for the addition of liver extract or vitamin B_{12} for the protection afforded the nervous system by these agents where such protective or therapeutic action is indicated.

The following are quotations from the editorial cited: "That folic acid does not offer neurologic protection to patients with pernicious anaemia is clear, but that it actually does harm to nervous system tissue directly appears to have been disproved. Folic acid may even be used safely in typical cases of pernicious anaemia, for maintenance, provided that liver extract is also used." The editorial goes on to point out the great usefulness of folic acid in the treatment of atypical, tropical, megaloblastic anaemias, and the megaloblastic macrocytic anaemias of infancy. We quote: "'Achrestic' anaemia and the 'refractory' megaloblastic anaemias described by Davidson seem to respond better to folic acid (referring to the effectiveness of liver extract and vitamin B_{12} in these cases). Thus, this chemical appears to have earned a definite place as a useful drug, although its exact relations, if any, to vitamin B_{12} require further elucidation."

In the same issue of the *New England Journal of Medicine* there appears an article from the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, by Harvey, Howard, and Murphy, who concur with the opinion of the editorial we have cited. These investigators treated 40 subjects with 20 mg. of folic acid daily for three to twelve months. They say, "None of the subjects demonstrated spinal cord or peripheral nerve damage during the period of treatment. This confirms other recent studies and supports the accumulating evidence that folic acid does not have a toxic effect on the central nervous system of persons without pernicious anaemia. In the February, 1950, issue of *Blood* Drs. Weissberg, McGavack, Vogel, and Kenigsberg of the Metropolitan Hospital Research Unit of the New York Medical College report that folic acid has no harmful effects on the central nervous system. These physicians investigated 26 persons who were normal or who had some form of neural changes not associated with anaemia. Each person was given 20 mg. of folic acid daily. The period of treatment was from six to twelve months, with the average at ten months.

From the observations cited above we would submit, then, the following conclusions: (1) Folic acid is a valuable medicament in the treatment of anaemias, being especially useful in refractory, achrestic, atypical macrocytic types of anaemia exemplified by the megaloblastic anaemia of infancy, tropical anaemias, the so-called "pernicious anaemia of infancy," and sprue; (2) that in many of these anaemias folic acid brings about a normal peripheral blood picture and favourable marrow responses in a way which is superior to the effect of liver extract or vitamin B_{12}; (3) that folic acid does not *per se* play any causal role in neurological damage, nor does it have a toxic action; but (4) that folic acid should not be used with the anticipation of correcting or preventing the neurological lesions associated with pernicious anaemia, but that liver extract or vitamin B_{12} should be used in addition to folic acid where this therapeutic action is needed. We respectfully submit the above observations in the hope that they will receive attention and that they will be useful in the clarification of the proper role to be played by folic acid in the treatment of disease.—I am, etc.,

RUTLEDGE W. HOWARD,
Director of Professional Service, Lederle Laboratories Division, American Cyanamid Company.

New York.

Cancer of the Respiratory System

SIR,—There has been a steady and progressive increase in the number of deaths from cancer of the respiratory system in men and women in recent years. The Registrar-General's returns for England and Wales are as follows:

	Males	Females
1937	4,089	1,162
1942	5,596	1,525
1943	6,094	1,581
1947	8,603	2,019

In the annual returns of the Medical Officer of Health for Manchester for the years 1937 to 1946 inclusive, the increases were from 133 to 188 in males and 23 to 45 in females. In 1949 it affected 234 males and 49 females. Leading British insurance companies have been impressed by an increase of bronchial cancer in their death claims. These increases are probably due, to some extent, to more careful and accurate diagnosis of diseases of the lungs, but there are other probable reasons for them.

There has been a great increase in cigarette smoking since the 1914–18 war, and especially by women. The Board of Trade returns show that the total weight of all forms of imported tobacco in millions of pounds rose from 114 in 1910 to 356 in 1919. In succeeding years it varied in amount, especially during the second world war, and in 1946 it was 434 million pounds.

In American opinion the incidence of diagnosed cases of bronchial carcinoma is increasing at a rate which appears to be faster than that of other diagnosed tumours. Tobacco smoking as a cause has received particular attention there because of the great incidence of carcinoma of the lung in males as compared with females. It occurs chiefly in heavy smokers and especially from 40 to 70 years of age. In 330 post-mortem examinations 78% were of men and 21.9% women. The life tables prepared by Pearl in America have a bearing on this point; he gave these, from the age of 30, for 6,813 individuals—non-smokers, moderate, and heavy smokers—and found that only 30.4% of heavy smokers lived to 70.

There is much tar-containing soot in the Manchester atmosphere from domestic and commercial fires, and in recent years this has been added to, as elsewhere, by the black exhaust of Diesel-engine buses and other heavy vehicles. A sample of this was found to contain 3% of a tarry oil which produced epithelioma of the skin on laboratory mice. There was no evidence found at Manchester that inhalation of this exhaust tar can cause cancer of the lungs, as laboratory animals could not be exposed to it for long enough periods for more than bronchial irritation to be obtained.—I am, etc.,

Manchester. E. M. BROCKBANK.

Morphine in Bronchial Asthma

SIR,—Dr. A. G. Ogilvie does not quote me correctly in his letter (July 29, p. 300). I did not write that "the use of morphine in severe asthma is justified because sedation is urgent." I stated that morphine is justified if other means of sedation have failed, and then only if its depressant and—probably histaminic—broncho-constrictor actions are compensated by adrenaline. I do not agree with Dr. Ogilvie that the asthmatic who has had morphine will not respond to adrenaline. Naturally, an effective dose of adrenaline is necessary, and if the patient is tolerant to it (tolerant to *any* dose of it) morphine would be as dangerous as it is without adrenaline. I do not see why Dr. Ogilvie wants to exclude morphine from use in asthma without any exception: that its injudicious use is dangerous is no valid reason. All that is necessary is that the medical practitioner is aware of the danger and of his responsibility.—I am, etc.,

London, W.C.1. H. HERXHEIMER.

Deaths in Breech Deliveries

SIR,—Dr. T. Redman (April 8, p. 814) showed that in breech deliveries the combined foetal and neonatal death rate is irrespective of parity and type of breech. Some statistics from Sorrento Maternity Hospital, Birmingham, may be of interest in this connexion. From 1945–9 inclusive, out of a total of 9,225 deliveries—excluding twins, malformations, and babies weighing less than 5½ lb. (2.5 kg.)—there were only 178 breech deliveries. The results are summarized in the following tables:

TABLE I.—*With Legs Flexed*

	Number	Stillbirth, With Cause	Neonatal Deaths, With Cause	Combined Foetal and Neonatal Mortality Per cent
Primigravidae	13	0	0	0
Multiparae ..	23	3 (1 prolapsed cord 2 intracranial birth injury)	1 (intracranial birth injury)	17

TABLE II.—*With Legs Extended*

	Number	Stillbirth, With Cause	Neonatal Deaths, With Cause	Combined Foetal and Neonatal Mortality Per cent
Primigravidae	88	1 (cord tight round neck; died during 1st stage labour)	4 (1 atelectasis, 1 haemorrhagic diathesis, 2 intracranial birth injury)	6
Multiparae ..	54	2 (intracranial birth injury)	0	4

Owing to the infrequency of breech deliveries, it has become very difficult for midwives and general practitioners to be taught and to keep in practice. In addition, to minimize foetal and neonatal deaths an expert team is required for the delivery, as stressed by L. Cox.[1]

The diagnosis must obviously be made prior to term so as to ensure hospital delivery and also to enable the size of the pelvis to be carefully assessed, if necessary by *x*-ray pelvimetry. To avoid an excessively large baby, labour should be induced at term and, occasionally, shortly before. Frequently, surgical induction will be required, but by using the Drew Smythe catheter a bag of forewaters can be left with advantage. This method was used in 48 of the above cases.

At Sorrento Maternity Hospital better results have been obtained recently, shown by no foetal or neonatal deaths during the first six months of this year, and only one during 1949. This was a foetus with a flexed breech, the third pregnancy of a woman with a flat pelvic brim. The improvement is largely due to the routine use of pudendal block anaesthesia in all primigravidae, as well as an episiotomy when the foetal buttocks distend the perineum. The resultant pelvic floor relaxation facilitates delivery to a marked degree. The anaesthesia results in good co-operation of the patient, so that she is more likely to keep her buttocks well over the edge of the bed when in the lithotomy position, and so ensure that the baby's body can hang and aid flexion of the after-coming head. Any shoulder manipulation can be performed painlessly, without further anaesthesia, and the occiput rotated anteriorly if necessary, the Mauriceau–Smellie–Veit grip being preferred. Should there still be difficulty with the head—if disproportion is prevented this should be rare—forceps can usually be applied without further anaesthesia.

The prime object of this letter is to urge that the time has come for revision of the Central Midwives Board rules regarding breech deliveries. Every breech should be considered as an abnormality, medical aid sought, and hospital delivery ensured. In hospital, a delivery team is necessary. Pudendal block anaesthesia is a great advantage in primigravidae.—I am, etc.,

Birmingham, 13. JEAN L. HALLUM.

REFERENCE

1 Cox, L., *J. Obstet. Gynaec. Brit. Emp.*, 1950, **57**, 197.

Myeloid Leukaemia and Pregnancy

SIR,—As Drs. L. M. Edwards and H. D. Freeth (July 22, p. 199) found that there are few records of pregnancy in myelogenous leukaemia, the following brief case notes may be of interest to them.

A woman, aged 36, was admitted to the Meath Hospital, Dublin, in August, 1947, with gross splenic enlargement, which was found to be due to myelogenous leukaemia. She had deep *x*-ray therapy to the spleen, ending on August 22, 1947. The white blood count began to rise in December, and by the end of February, 1948, she needed further deep *x*-ray treatment, which was completed on March 8. In July she was given a third course of deep *x*-ray therapy. At the end of October she was found to be pregnant, and her white-cell count was 62,200. She was given a further course of *x*-ray treatment in January, 1949, and a normal baby was born on May 1. The baby, now 14 months old, is a normal, well-grown, and healthy child. The mother had to have further *x*-ray treatment in October, 1949, and is still keeping quite reasonably well.

It is interesting to note that pregnancy occurred after three courses of deep *x*-ray therapy and that a course given during pregnancy had apparently no ill-effects on mother or baby.—I am, etc.,

Dublin. BRENDAN O BRIEN.

Diphyllobothrium Infestation

SIR,—The very full article by Drs. J. C. Harland, J. G. Humble, and P. G. Mann (July 22, p. 188) upon diphyllobothrium infestation in Great Britain encourages a brief report of a case met with in 1936.

The patient, a man at that time aged 43, had spent part of the first world war in Northern Europe and admitted later that he and his Army colleagues had often caught and eaten fish somewhat inadequately cooked. He had been diagnosed as having pernicious anaemia in 1923 and treated with liver for many years before he was seen in 1936. In that year he had a macrocytic hyperchromic anaemia: haemoglobin 112%, and r.b.c.s 3.8 million. The differential white cell count showed 4% eosinophils. He complained of a bad taste in his mouth, flatulence, occasional bouts of diarrhoea, and borborygmi. Treatment for his anaemia failed to produce a normal blood picture, and examination of his stools showed scanty ova of diphyllobothrium.

The worm was obtained, head and all, by the use of filix mas. Subsequently his red blood count rose to normal, but his eosinophilia actually increased and continued between 6% and 11% for eighteen months afterwards. The test meal showed that he was achlorhydric. Ova were never found again in this man's faeces and he appeared to be the host of only one worm.

—I am, etc.,

London, W.1. F. HARWOOD STEVENSON.

Obituary

E. CRANMER HUGHES, O.B.E., M.Chir., F.R.C.S.

Mr. E. C. Hughes, consulting surgeon to Guy's Hospital, died at Pembury, Kent, on July 28 aged 71.

Ernest Cranmer Hughes was educated at Marlborough and Clare College, Cambridge, and went to Guy's Hospital in 1901. He qualified in 1904, took the F.R.C.S. in 1906, and M.Chir. of the University of Cambridge in 1907. He was appointed assistant surgeon to Guy's Hospital in 1911, full surgeon in 1932, and consulting surgeon on his retirement in 1938. He served on the Court of Examiners of the College from 1930 to 1940, and also examined in the Universities of Cambridge and Birmingham. In the first world war he was a captain in the R.A.M.C., and was consultant surgeon to Queen Mary's Royal Naval Hospital at Southend-on-Sea. On the outbreak of the recent war he was appointed surgeon to the E.M.S. hospital at Pembury, near Tunbridge Wells, and when the medical school of Guy's was evacuated to Pembury he became once again the chief teacher in surgery of the undergraduates of his old school. Throughout the war, and up till 1947, he operated and taught at Pembury and at the same time conducted a weekly teaching round at Guy's.

As a young man Hughes came under the influence of two very great surgeons: he was house-surgeon to Arbuthnot Lane and assistant surgeon to F. J. Steward, and throughout life he carried on Lane's clean, careful technique and Steward's clinical wisdom. He wrote little, his publications being for the most part lectures on clinical subjects. He will, however, be remembered by all who came in contact with him for his personal charm, his sunny disposition, his complete inability to speak or think unkindly of anyone, and his wonderful gift of bedside teaching and of expounding the simplest things in telling phrases that fixed them permanently in the minds of his students. To many generations of Guy's men, and to those surgeons who worked with him or were examined by him during the years that he served on the Court of Examiners of the Conjoint Board, he was known affectionately as Joey Hughes. He was a wonderful teacher, a wonderful examiner, and a well-loved colleague. He is survived by his widow and a son and a daughter.—H. O.

E. T. JENSEN, M.B.

Dr. E. T. Jensen died suddenly in London on July 31 at the age of 76. He was co-founder of the Institute for the Scientific Treatment of Delinquency and chairman of its council until his death.

Ernest Thomas Jensen studied medicine at Guy's Hospital. He graduated M.B. in 1901. In his early days he held several posts. At one time he was civil surgeon to the Herbert Hospital, Woolwich. He served with the Field Force in the Boer War, and later he went as the medical officer to an expedition into unexplored parts of East Africa. Throughout his professional life he exhibited a catholic interest in many branches of medicine.

We are indebted to Dr. Edward Glover for the following appreciation: Dr. Jensen will be remembered not so much for his strictly medical services as for the part he played in founding and developing the Institute for the Scientific Treatment of Delinquency. The psychological study of criminal conduct is of comparatively recent growth, and even yet lags behind other branches of medico-psychological investigation. As is so often the case, much of the impetus to research came from without, in this case from persons whose primary interest was in social reform rather than in clinical and social psychology. When Dr. Jensen first interested himself in this field, little or no systematic work had been done on the subject. A happy association with Dr. Grace Pailthorpe, who in the early 'twenties had pursued a research on prison populations, led to the formation of an organizing committee under the chairmanship of Dr. Jensen. Soon the services of a number of medical psychologists were enlisted, and the Institute for the Scientific Treatment of Delinquency was formed. An embryo clinic, housed at first at Dr. Jensen's own residence and later given a roof by the West End Hospital for Nervous Diseases, soon acquired a regular organization and home of its own under the name of the Psychopathic Clinic. After 16 years of work, uninterrupted by war, this was taken over in 1948 by the National Health Service and now functions as the Portman Clinic: I.S.T.D.—a special out-patient centre dealing yearly with well over 400 cases of pathological crime. Throughout this period Dr. Jensen supported the organization with unflagging zeal and, once the clinic was taken over, devoted his attention to expanding the existing Institute for the Study and Treatment of Delinquency, which remains a private enterprise engaged in numerous teaching, publishing, and research projects.

Those who had the opportunity of working with Dr. Jensen were quick to recognize his personal qualities, a quiet courtesy and humour, fertility of resource in difficulty, and an almost boyish optimism which could not be shaken by any reverse. The breadth of his cultural interests —he was in private life an art connoisseur of note—could not be mistaken. He was a man of distinguished, almost ascetic, cast with a somewhat frail stooping figure. His memory will long remain with those colleagues who worked with him in what proved to be a pioneering experiment in social medicine and which in fact remains a lasting tribute to his unquenchable spirit.

Dr. Grace W. Pailthorpe writes: Although a lifelong friend, Dr. Jensen and I came together in our medical work in 1931, when I had completed a research for the Medical Research Council on the "Psychology of Criminals." Because my colleagues were impressed with my research findings, I was encouraged to feel that something should immediately be done. This led me to approach Dr. Jensen with the idea of founding a body to deal with delinquency both scientifically and clinically. In May, 1931, he and I founded the Institute for the Scientific Treatment of Delinquency. For the following six years his home at 56, Grosvenor Street housed the institute. As chairman from its inception till his death he gave his time and money freely, and to him as well as to myself came the satisfaction of seeing the work well rewarded by results. In 1937 the I.S.T.D. at last was able to house itself, and moved from Dr. Jensen's home to Portman Street. But unfortunately this change was not to last: during the war the Portman Street house was bombed, and Dr. Jensen again came forward with his assistance until the I.S.T.D. was finally accommodated in its present quarters at 8, Bourdon Place, Mayfair.

During the last war, old as he was, he was in London actively taking part in tending air-raid casualties. His publications were relatively few. His modesty accounted for this, for he would often prepare a paper for publication which his colleagues thought of value but which he could not feel had reached the point of perfection which he demanded of himself. This need for perfection was due to his highly developed aesthetic sense. To the day of his death

his vitality, his joy in his work, and his love of his fellows were among his outstanding features. His death brings sorrow and a void in the hearts of all those who knew him intimately, whether as patient, medical colleague, or friend.

HENRY FAITHFUL SMITH, who died on July 12, was born, in his own words, of South Saxon stock, the younger son of Dr. J. A. Smith, vicar of Swansea and later dean of St. David's. He was educated at Repton and Oxford, and after farming for a few years in Canada began to study medicine at Edinburgh University in 1904, when he was about 10 years older than most of his fellow students. He graduated M.B., Ch.B. in 1909, and after acting as house-physician to the late Sir Byron Bramwell he settled in partnership in a practice at Windermere, his old chief describing the terms as "not a deed of partnership but an agreement between gentlemen." He proceeded M.D. in 1913. In the first world war he served in the R.A.M.C. in Mesopotamia, where he won the reputation of always knowing his own mind and acting with promptitude and decision. He had a most strict sense of duty, and from his duty no power on earth could make him swerve. He could turn his hand to most things. He returned to his Windermere practice and remained there, a doctor much beloved. Dr. Smith's last professional work was done as chairman of the Kendal recruiting medical board during the last war. Then he retired to Gower, the place of his boyhood, and there, after a laryngotomy performed in London, he died. He had unusual physical toughness, and even in his seventies could tramp the fells all day and walk his juniors off their legs. He was a devoted golfer, and almost his only sedentary recreation was bridge. He was no intellectual, but he had an abounding common sense. He was a survival of the God-fearing Victorian Englishman and a gentleman in the tradition of Charles Kingsley, and he will be missed.—J. W.

Medico-Legal

A DOCTOR EXONERATED

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

A man who was demobilized from the Army in 1945 suffered from chronic rheumatism, for which his doctor treated him. The diagnosis was confirmed by various specialists. In January, 1948, he returned home from work feeling very ill, and late in the evening he collapsed. His wife telephoned to the doctor and asked him to come to the home, but the doctor did not do so, and prescribed sedatives. In the early morning she asked a policeman to call the doctor again, and at 4 a.m. he came and arranged for the patient to go into hospital, where he was operated upon for a perforated gastric ulcer. He died the following morning. His wife sued the doctor, Dr. John D. Hempseed, of Sheffield, at Yorkshire Assizes for negligence.[1] In defence the doctor gave evidence that at no time had the patient ever complained of stomach pain, but rather of pains of the shoulders, legs, arms, and lumbar region. He had understood the wife to say over the telephone that the husband was suffering from the "usual" pains; she had not mentioned the stomach. Her counsel then said that he was no longer prepared to submit that the doctor should have diagnosed a gastric ulcer, but maintained that he had been unskilful in not attending the patient when he was first summoned.

Mr. Justice Hilbery said in giving judgment that he was satisfied that there had never been any complaint of abdominal pain or sign of abdominal disturbance. It would, he added, be a shocking thing if in the circumstances the court were to hold that a medical man was guilty of negligence because he did not rush round immediately. He entered judgment for the doctor with costs.

[1] *Yorkshire Post*, April 21, 22.

Universities and Colleges

UNIVERSITY OF DURHAM

The following candidates have been approved at the examinations indicated:

M.D.—C. B. Henderson, C. Josephs, G. S. Michelson, W. Walker, J. E. Wilson, W. K. Yeates.

FINAL M.B., B.S.—J. Anderson (with second-class honours), A. King (with second-class honours), Jean Armstrong, J. S. Bearcroft, Dorothy G. Blackett-Ord, Mary A. Brennan, I. S. Brown, H. Byrne, R. Carr, Joan M. Cashman, A. Chesshire, D. B. Clough, Irene Colbert, Greta I. Drummond, Ola E. P. During, M. Graham, R. P. Graham, Mary E. S. Gray, K. Hardy, R. J. Harris, Anne H. Harrison, W. R. Heeler, J. G. Hindmarsh, K. W. Holt, G. Hurst, P. Hutchinson, Audrey Jennings, B. O. Kawala, Joyce L. Kemp, June M. Kirk, J. C. Knox, G. B. Lawrence, Hilda M. McCormick, J. A. McCraith, M. J. Morgan, Elizabeth Nicholson, J. D. Rickinson, C. Robertson, D. Russell, C. Shadforth, Monnica C. Stewart, K. A. Stone, N. Thompson, T. A. Trotter, D. M. Turnbull, K. E. Wardill, Joyce M. Watson, F. J. Wilkinson, B. Zimet.

D.P.H.—A. Forster, W. B. A. Smyth.

UNIVERSITY OF LONDON

Sir Archibald Gray has been appointed by His Majesty in Council as a member of the University Court from October 1 for the remainder of Sir Henry Dale's term of office—i.e., 1948–53.

Sir Alexander Fleming, F.R.S., will represent the University at the fifth International Congress of Microbiology to be held at Rio de Janeiro from August 17 to 24.

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Professor Dorothy Russell (Institute of Ophthalmology); Professor W. J. Hamilton (second representative, Royal Veterinary College); Major-General P. H. Mitchiner (Territorial and Auxiliary Forces Association of the County of London); Dr. A. Topping (University College Hospital).

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *Middlesex Hospital Medical School:* Dr. A. C. Thackray (Pathology); Dr. F. C. Golding (Radiology); Mr. Rainsford Mowlem and Mr. T. Holmes Sellors (Surgery). *Westminster Medical School:* Dr. I. W. Magill and Dr. G. S. W. Organe (Anaesthetics); Dr. J. G. Humble and Dr. B. W. Lacey (Bacteriology); Dr. I. McA. Anderson (Children's Diseases); Dr. G. D. Lumb and Dr. A. D. Morgan (Pathology). *Royal Free Hospital School of Medicine:* Dr. Nuala F. T. Crowley (Bacteriology). *King's College:* Dr. J. P. Quilliam (Pharmacology). *Institute of Psychiatry:* Dr. K. Cameron (Mental Diseases). *Institute of Obstetrics and Gynaecology:* Dr. V. B. Green-Armytage (Obstetrics and Gynaecology). *Guy's Hospital Medical School:* Mr. R. O. Holland, M.R.C.S., L.R.C.P., L.D.S. (Dental Surgery). *St. Thomas's Hospital Medical School:* Dr. J. F. Ryan (Anaesthetics).

The South Middlesex Fever Hospital, Isleworth, has been added to the list of institutions at which students may take the course in fevers for the M.B., B.S. degrees.

The following candidates have been approved at the examinations indicated:

M.D.—*Branch I (Medicine):* Daphne S. A. Anderson, P. G. Arblaster, G. Beven, E. P. Bharucha, D. P. Bowler, P. D. Bryant, G. B. Carruthers, Betty L. Coles, J. B. Cook, J. N. C. Cooke, Rosemary Davies, D. M. Douglas, H.-J. B. Galbraith, R. F. Griffith-Evans, A. G. S. Grimble, D. B. Gunasekara, H. C. Hamilton, E. P. W. Helps, H. D. G. Hetherington, F. C. N. Holden, Mary C. Holt, O. A. N. Husain, S. L. O. Jackson, J. W. M. K. W. S. Jayewardene, I. D. MacDonald, W. Mackenzie, J. G. Millichap, J. C. Mitchell, Madeleine B. Morris, *W. O'Brien, Ethel A. Perrott, *F. I. Rackow, G. S. Ratnavale, R. B. Sloane, Margaret H. Stanfield, Kathleen Staynes, *J. S. Stead (*University Medal*), B. E. R. Symonds, G. I. Tewfik, J. L. G. Thomson, D. Q. Trounce, R. B. N. Wilsdon, B. B. Zeitlyn. *Branch II (Pathology):* J. D. Abbott, D. N. Baron, A. R. Blowers, B. S. Cardell, M. C. H. Dodgson, R. J. Evans, H. P. Ferreira, A. K. Mant, A. F. Mohun, D. S. Ridley, H. Sterndale, Elizabeth Topley. *Branch III (Psychological Medicine):* J. P. Crawford, M. Hamilton. *Branch IV (Midwifery and Diseases of Women):* H. D. Freeth, F. Kohiyar, F. C. R. Picton, G. J. Sophian. *Branch V (Hygiene):* L. R. L. Edwards, H. T. Phillips, Alison D. McDonald, G. H. Stuart, W. C. Turner. *Branch VI (Tropical Medicine):* S. Fernando.

*Mark of distinction.

No. 29

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended July 22.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	38	2	22	1	—	17	1	12	—	—
Deaths		—	1				—	—		
Diphtheria	46	4	13	2	3	104	22	16	2	7
Deaths	1	—	—	—	—	1	1	—	—	—
Dysentery	166	8	109	—	2	68	8	33	2	2
Deaths					—				—	—
Encephalitis, acute	14	4	—		—	2	—	—	—	—
Deaths		1		—			—			
Erysipelas			21	4	—			17	4	3
Deaths										
Infective enteritis or diarrhoea under 2 years				23					71	
Deaths	20		2	1	4	22	2	8	1	1
Measles*	8,754	601	197	229	75	5,376	490	149	204	102
Deaths†		—	—	—	—			—	1	—
Ophthalmia neonatorum	37	2	13	1	—	54	—	12	—	—
Deaths										
Paratyphoid fever	5	—	—	7(B)	—	50	—	1(A) 2(B)	—	1
Deaths	—		—		—	1	—	—	—	—
Pneumonia, influenzal	293	17	5	—	3	330	24	2	1	1
Deaths (from influenza)‡	6	1	1	—	—	6	—	—	—	—
Pneumonia, primary			110	¶				123	27	
Deaths	114	24		4	3	126	9		2	4
Poliomyelitis, acute	260	28	58	5	18	117	13	3	1	2
Deaths§	13	3		—		9	1			
Puerperal fever		—	6				—	6		—
Deaths										
Puerperal pyrexia‖	94	7	9	—	2	105	11	3	—	1
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,153	67	98	53	50	1,043	66	105	74	32
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—		—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	6	—	1	1	—	6	—	1	4	—
Deaths	—	—	—		—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,881	303	205	86	23	2,184	84	33	100	76
Deaths	2	—	—	—	1	9	—	3	—	—
Deaths (0–1 year)	207	27	38	16	15	275	43	29	17	9
Deaths (excluding stillbirths)	4,092	611	550	146	108	4,228	678	496	146	91
Annual death rate (per 1,000 persons living)			11·0					9·9	9·0	
Live births	6,758	1142	913	443	235	7,608	1223	866	411	209
Annual rate per 1,000 persons living			18·3					17·4	25·5	
Stillbirths	181	29	22			182	20	19		
Rate per 1,000 total births (including stillborn)			24					21		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications in the week ended July 29 were: paralytic, 197 (189); non-paralytic, 108 (71); total, 305 (260). The figures for the previous week are shown in parentheses. It is perhaps satisfactory that the main increase—37—occurred in the non-paralytic types and only 8 in the paralytic, and that the proportion of the former for the week under review increased to 35.4% of the total notifications.

The four counties London, Warwick, Lancaster, and Stafford contributed one-quarter of the total notifications for England and Wales, compared with 46% in the previous week.

The more important increases in the week under review were as follows:

	Paralytic	Non-paralytic
Warwick	12	1
Essex	(1 less)	7
Gloucester	(3 less)	8
Leicester	6	5
Middlesex	8	3
Isle of Wight	4	3
Total	26 net	27

Total 53 (reduced to 45 for England and Wales by excess of decreases over increases elsewhere).

Attention has been focused in the past week on a relatively serious outbreak in the village of Digby, near Sleaford, Lincs. In this village, with its population of some 400 people, there have been 15 confirmed cases since July 10, and on August 8 there were 4 suspects under observation. The main weight of the attack fell on a new housing estate of 32 houses and 130 inhabitants, in which 11 confirmed cases occurred, including 2 deaths. The situation was improving by August 8 in that there had been no cases on the estate since August 5, although two or three of these suspect cases had developed after August 5 elsewhere in the Digby village area.

A small defect in the drainage system suggested the possibility of contamination of the water supply on the estate, but further investigations appear to have eliminated this possibility, and the evidence points to the spread of the disease in the community by ordinary contact infection from the first case, the onset of which was on July 10. Detailed epidemiological inquiries are being carried out, but the results are not yet available.

Anthrax in Cattle

In the outbreak of anthrax in cattle at Holme Pastures, Sutton-on-Trent, Nottinghamshire, 13 cattle had died by August 5. By the previous week-end 9 had died. Bacteriological proof has been obtained in 5 cases. About 150 cattle are exposed to risk in the area, and measures to prevent spread of infection have been carried out.

Discussion of Table

In *England and Wales* there were decreases in the notifications of measles 541, whooping-cough 236, dysentery 56, scarlet fever 22; while the only increase of any size was 48 for acute poliomyelitis. The incidence of scarlet fever remained practically constant in every area of the country, the only exception being a decrease of 41 in Lancashire. The largest local changes in the incidence of measles were decreases in Lancashire 164 and Yorkshire West Riding 123. Notifications of diphtheria fell by 10 in Lancashire.

In contrast to the general trend the incidence of whooping-cough in London and the surrounding counties increased during the week, the largest increases being in London 47, Surrey 45, and Middlesex 32; the largest decreases were in Lancashire 83, Gloucestershire 51, and Norfolk 51. The largest returns of dysentery were Lancashire 61 (Preston C.B. 15, Oldham C.B. 14, Littleborough U.D. 8); Yorkshire West Riding 28 (Bradford C.B. 8); Derbyshire 12 (Belper U.D. 11).

The rise in cases of acute poliomyelitis continues, 1,195 cases having been notified during the past eight weeks, compared with 496 in 1949, 228 in 1948, and 599 in 1947 for the corresponding period. The largest increase during the week occurred in London, where the cases rose from 8 to 28. Twelve of the 28 boroughs reported a case, and the largest returns were

Lambeth 5 and Woolwich 5. In Northumberland the cases fell from 16 to 8. Other large returns were Warwickshire 43 (Birmingham C.B. 28, Sutton Coldfield M.B. 5); Lancashire 24 (Manchester C.B. 8, Liverpool C.B. 6); Staffordshire 24; these cases were notified from 11 administrative areas. Worcestershire 13 (Dudley C.B. 5); Essex 13 (West Ham C.B. 5); Yorkshire West Riding 12, involving 9 administrative areas; Gloucestershire 11 (Bristol C.B. 7).

In *Scotland* increased notifications were reported for dysentery 22, acute primary pneumonia 14; decreases were reported for measles 70, whooping-cough 35, and acute poliomyelitis 9. A small rise in the incidence of dysentery occurred in every area, the largest returns being Glasgow 58 (an increase of 26) and Edinburgh 12. Notifications of acute poliomyelitis in Glasgow rose from 15 to 25, and the next largest returns were Fife county 7 and Angus county 4.

In *Eire* there were decreases for measles 92 and scarlet fever 23, while the only rise was whooping-cough 24. A decrease of 28 for measles and an increase of 11 for whooping-cough were recorded in Dublin C.B.

In *Northern Ireland* notifications of measles decreased by 53. This was due to a fall of 44 in the number of cases in Down county and 19 in Belfast C.B., where 12 of the 18 cases of acute poliomyelitis were also notified.

Week Ending July 29

Notifications of infectious diseases in England and Wales during the week included scarlet fever 1,012, whooping-cough 3,714, diphtheria 42, measles 8,291, acute pneumonia 277, acute poliomyelitis 305, dysentery 166, paratyphoid fever 7, typhoid fever 10.

Medical News

Royal College of Surgeons

The Honorary Medal of the Royal College of Surgeons of England has been awarded to Lord Webb-Johnson, in recognition of his many generous acts and continued labours in the interest of the college throughout the eight years of his presidency.

Travelling Fellowship Offered

The American Association for Thoracic Surgery has created a travelling fellowship (value approximately $1,000) for the study of thoracic surgery or its related sciences in the U.S.A. or Canada. The fellowship will be an annual appointment, and the American Association has generously invited the Society of Thoracic Surgeons of Great Britain and Ireland to nominate the first holder. Anyone interested in this fellowship is advised to communicate with the honorary secretary of the Society of Thoracic Surgeons, Mr. O. S. Tubbs, 15, Upper Wimpole Street, London, W.1.

Raymond F. Longacre Award

The Raymond F. Longacre Award for 1949 has been presented to Sir Charles Symonds by the Aero Medical Association of America. The award is given annually by the association to the person who has contributed most to the advancement of neuropsychiatric aspects of aviation medicine, including the development of aptitude tests for flying. The first award was presented to Dr. Ross A. McFarland in 1947 and the award for 1948 was made to Dr. Detlev W. Bronk. The presentation was made in London by Group Captain Corbett, of the Royal Canadian Air Force.

Delinquency

The Institute for the Study and Treatment of Delinquency has begun publication of a new quarterly, the *British Journal of Delinquency*, the main purpose of which is to enable students of criminology to keep in touch with recent developments in the various branches of science concerned with the investigation, treatment, and prevention of delinquency. While clinical contributions will receive special consideration, it is intended also to publish articles on medical psychology, psychiatry, psycho-analysis, organic medicine, educational psychology, sociology, economics, anthropology, psycho-biology, and statistics. The journal is published by Baillière, Tindall and Cox, and the annual subscription is £1 7s. 6d.

Japanese Journal of Biochemistry

The *Journal of Biochemistry*, organ of the Japanese Biochemical Society, has restarted publication. Founded in 1922, the journal was discontinued in 1944. In the past it has published many important papers by Japanese biochemists. It will appear quarterly from the Institute of Biochemistry, Tokyo University.

COMING EVENTS

World Federation for Mental Health

The third annual meeting of the World Federation for Mental Health will be held at the Cité Universitaire in Paris from August 30 to September 7. The discussions have been designed to lead up to the work of the next International Congress on Mental Health, which will take place next year. They are concerned with mental health in education, in industry, and among transplanted and homeless persons. A further subject of discussion will be that of leadership and authority in local communities. It is understood that the Government of Mexico has invited the International Congress to hold its meeting there in December, 1951.

Conference on Venous Disorders

A conference on venous disorders will be held at Aix-en-Provence on September 15–17 under the presidency of Professor René Leriche. Particulars may be obtained from the Secrétariat, Journées Internationales de Phlébologie, 4, Cours Mirabeau, Aix-en-Provence, France.

American Public Health Association

The 78th annual meeting of the American Public Health Association, and meetings of 32 related organizations in the field of public health and preventive medicine, will be held in Kiel Auditorium, St. Louis, Missouri, on October 30–November 3. The programme will be published in the September issue of the *American Journal of Public Health*. Additional information may be obtained from Dr. Reginald M. Atwater, executive secretary, American Public Health Association, 1790, Broadway, New York 19, N.Y., U.S.A.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, August 15, 4.30 p.m., "*The Anatomy of the Bile Ducts*," by Professor John Kirk.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barber.—On July 25, 1950, at Johnstone House, Belfast, to Nan, wife of Dr. J. M. Barber, a son.

Holliman.—On July 31, 1950, at University College Hospital, London, W.C., to Catharine (formerly Large), wife of Dr. Arthur Holliman, a daughter—Catharine Margaret.

Ritch.—On July 27 1950, to Dr. Elsie (formerly Morison), wife of Dr. Donald R. S. Ritch, "Dunholme," Stamfordham, Newcastle-upon-Tyne, a son.

Scadding.—On July 27, 1950, to Mabel, wife of Dr. J. G. Scadding, F.R.C.P., a daughter.

Starey.—On July 30, 1950, at Churchill Hospital, Oxford, to Phyllis (formerly Horton), wife of Dr. C. J. H. Starey, of Stokenchurch, Bucks, a son.

Taylor.—On July 29, 1950, in East London, South Africa, to Andrée, wife of Dr. W. Norman Taylor, of Fort Hare, Cape Province, a son.

Thomson.—On July 31, 1950, in Ashleigh Nursing Home, Newcastle-upon-Tyne to Elizabeth (formerly McCarn) and Dr. Donald Thomson, Glenroy, Stanhope, Co. Durham, a daughter.

White.—On July 25, 1950, at Mayday Hospital, Croydon, to Margaret White, M.B., D.Obst.R.C.O.G. (formerly Stather Hunt), and Thomas White, M.B., M.R.C.O.G., a daughter.

MARRIAGE

Eyles—Cassells.—On July 12, 1950, in Norfolk, Reginald Eric Eyles, L.D.S. R.C.S., to Nulece Cassells, M.B., Ch.B.

DEATHS

Audland.—On July 31, 1950, at Witherslack Nursing Home, Westmorland, William Edward Audland, M.B.E., M.R.C.S., L.R.C.P., aged 90.

Bankes.—On August 1, 1950, at The Royal Masonic Hospital, Ravenscourt Park, London, W., John Herbert Bankes, M.R.C.S., L.R.C.P., aged 71.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Prematurity and Intracranial Injury

Q.—*I was told during my training that in order to prevent cerebral haemorrhage in premature infants it was necessary to avoid delay in delivering the shoulders. To do this, as soon as the head is born one hand is put inside, the shoulders rotated, delivered immediately, and the baby extracted. The reason given for this was that while the baby's head remains in utero and inside the vagina an even pressure is exerted on the skull. When the head is born there is an alteration in the pressure due to the sudden release of the head, and if the shoulders are not delivered immediately blood is forced down into the baby's brain and the force is sufficient to tear a blood vessel and cause a cerebral haemorrhage. I have never seen this theory in print. Is there any evidence to support it or not?*

A.—Babies born prematurely are undoubtedly more liable to intracranial injury and haemorrhage, and it is generally believed that their tendency to suffer intranatal asphyxia is a predisposing factor, although this acting alone is not likely to cause more than petechial cerebral haemorrhages. The release from compression which accompanies delivery of the head may play a part in some cases, possibly because it allows a resurgence of blood to the brain and meninges, but mainly because it results in a sudden change in the shape of the skull and an alteration in the strains to which the intracranial ligaments are exposed. The release phenomenon occurs no matter whether the shoulders follow the head quickly or slowly, and the writer has never previously heard it suggested that during the interval between the birth of the head and of the shoulders the intracranial vessels can become so engorged as to rupture spontaneously. Certainly this has never been proved and it can only be regarded as a theoretical possibility which is open to dispute. The congestion of the superficial tissues which is sometimes seen pending delivery of the shoulders does not necessarily mean that there is a similar change in the intracranial vessels. Moreover, in the premature baby the girth of the shoulders and trunk is very much less than that of the head, so that they not only tend to slip out easily and quickly but in the meantime are subjected to minimum pressure from the lower birth canal already stretched by the head. The tendency for the head to become congested is therefore less than in the case of the mature infant. One of the facts established beyond reasonable doubt is that the premature baby is ill-fitted to withstand manipulation during labour, and it would appear that manual rotation of the shoulders and extraction or expression of the trunk is potentially more dangerous than allowing the very short delay necessary for the delivery to be completed spontaneously.

In most cases intracranial injury leading to haemorrhage occurs before the delivery of the head, and in premature babies may be caused merely by the resistance of the vagina and perineum. It is now fairly well established that episiotomy appreciably reduces this risk. It may be added that, if there is anything in the argument put forward, episiotomy also ensures rapid and easy delivery of the shoulders without recourse to manipulations.

Coroners

Q.—*What system governs appointments to the office of coroner? By whom are such appointments made? Are they advertised, or is it customary to appoint the deputy already in office? How are coroners nominated, and what are the limits of income available from their office? Is any preference shown to an applicant with a legal qualification over one who is medically qualified? Are any such appointments given only to applicants possessing both medical and legal qualifications?*

A.—A county coroner is appointed by the county council, a borough coroner by the borough council (Coroners (Amendment) Act, 1926, s. 2). If the district of a county coroner is wholly within a county borough the appointment is made by the council of that borough (Coroners Act, 1887, s. 33; Municipal Corporations Act, 1882, s. 34 (4)). An appointing authority is not obliged by law to advertise a vacant coronership, but it is customary to advertise the more important appointments in the legal and medical journals and in the "Public Appointments" columns of the leading daily newspapers. It sometimes happens—but by no means invariably—that a deputy-coroner already in office is appointed to the vacant coronership. In such a case his experience and general suitability rather than the fact that he happened to be the deputy would be the deciding factor. Experience as a deputy, however, carries great weight—this is especially the case where the more important appointments are concerned.

It must be remembered that there are about 270 coroners in England and Wales, and that their coronerships vary very greatly in size and importance. At one end of the scale are the small country appointments where the remuneration amounts to not much more than a honorarium, and at the other extreme are the busy posts requiring the services of men who give their whole time to the duties of the office. Of recent years there has been a tendency for paying authorities to make a distinction between a coroner's basic salary and the amounts it allows him for the expenses incurred in carrying out his work. These allowances for expenses in some instances reach high figures. Thus the two whole-time coroners for the County of Middlesex are paid a salary of £1,500 and receive £1.000 for their expenses. In London the basic salary for a whole-time coroner is £1,600 and he receives £350 for defraying his costs. It must be understood that these sums are paid to the coroner for his personal expenses and have nothing to do with the reimbursements he receives for money paid out in connexion with his administrative or judicial duties. Between these two extremes coroners' salaries vary very widely and the variation does not always bear a constant relation to the amount of work done or the time involved in doing it. The pay of a deputy, or assistant deputy, is a matter of arrangement between himself and the coroner.

Since out of approximately 270 coroners the great majority are lawyers it would be reasonable to infer that a legal qualification is held to be more important than a medical qualification so far as fitness for the office is concerned. In London, and a few of the more important centres, the electing authority endeavours to limit the candidature to persons who possess both legal and medical qualifications. No coroner has been appointed in the county of London for the past thirty years who has not had the dual qualification. There are 13 whole-time coroners in England and Wales, of whom 10 are qualified in both law and medicine. These 13 coroners between them dispose of about one-third of all the cases reported in England and Wales during the year. Of the remaining 257 coroners, 16 have a medical (but no legal) qualification; and 241 are barristers or solicitors with no medical qualification.

Ps. pyocyanea Infection of Middle Ear

Q.—*A man had a chronic discharge from the middle ear. The organism cultured was Ps. pyocyanea. Is there any antibiotic which is active against this organism? Would C.T.A.B. applications be likely to help? What local treatment is indicated?*

A.—*Ps. pyocyanea* is remarkably resistant to both antiseptics and chemotherapeutic agents. Among the former none can be recommended for use in such a case as this. C.T.A.B. (cetavlon) has less action on this organism than on any other commonly concerned in sepsis. Penicillin is useless, and the newer antibiotics aureomycin and chloramphenicol are also generally powerless in the concentrations which can be attained at the site of infection. Streptomycin is the exception; the susceptibility of *Ps. pyocyanea* to this antibiotic varies, but it is usually such that the concentrations attainable by local application are effective. A solution of 5 mg. per ml. should be instilled into the ear several times a day: the drug may also be given intramuscularly, particularly during any surgical treatment which may be indicated. Authors reporting favourably on local streptomycin treatment for otitis media, some of whose

patients were infected with this organism, are Pulaski and Matthews (*Arch. Otolaryng.*, 1947, **45**, 503) and Harris and Finland (*North Carolina Med. J.*, 1947, **8**, 276).

Local treatment would consist in keeping the meatus as clean as possible, and in ensuring that the discharge was allowed a free exit from the middle ear. The first object is attained either by syringing with warm water, followed by dry mopping, or by dry mopping alone, twice daily; the second by removal of granulations with chromic acid, of polypi by a snare, and of debris by syringe or scoop.

Indications for P.A.S. in Pulmonary Tuberculosis

Q.—*What are the indications for the use of para-aminosalicylic acid? I have a patient, aged 22, with advanced pulmonary tuberculosis. She has persistently refused sanatorium treatment, still refuses it, and is beginning to go downhill now. Is it worth while prescribing P.A.S.?*

A.—The indications for this drug in the treatment of pulmonary tuberculosis may be briefly stated as (*a*) recent disease, and (*b*) in combination with streptomycin to prevent or delay the loss of sensitivity of the tubercle bacillus to the antibiotic. P.A.S. is effective only in those lesions in which there is an absence of fibrosis; it is therefore suitable in cases where there is evidence of recent spread of the disease. In chronic fibroid phthisis it has the temporary effect of creating a feeling of well-being, and some improvement radiologically may occur from the clearing up of recent foci of activity, but a state is soon reached beyond which no further improvement can be expected. In combination with antibiotics it is useful in the prevention of drug-fastness. There is also evidence that with the combined administration of streptomycin and P.A.S. patients improve more rapidly than when treated with streptomycin alone.

The treatment of the patient in question with P.A.S. depends very greatly on the character and chronicity of her lesion. However, it is probable that benefit would be derived from P.A.S. but the permanency of any good effects will depend on the clinical state of the patient.

Sensitization to Calf Lymph

Q.—*On February 17 I vaccinated a European baby of 20 months not previously vaccinated against smallpox. No immediate change was observed in the temperature, pulse rate, or respiration, though the same batch of calf lymph was found to be potent when used on control cases. Eight days later a series of papules appeared on the vaccinated leg; within 24 hours they changed first to vesicles and finally to pustules. During the next five weeks the same type of eruption was observed on the other leg and both arms. Very few were seen on the face and trunk. The child at no time ran a temperature and, apart from a slight inclination to scratch individual lesions, showed no signs of constitutional disturbance. This child, now in Nyasaland, will continue to reside in tropical areas in which smallpox is endemic, and it is important that a correct diagnosis should be established. If this was a case of generalized vaccinia, then I must issue a certificate to that effect to ensure that she is not vaccinated again. What is the likely diagnosis, and is revaccination advisable or not?*

A.—Although the information is not explicitly given it is assumed that the papules, vesicles, and pustules which appeared at the site of attempted vaccination were typical and were followed by the usual foveated scars and represented a successful vaccination. It is then necessary to go over the complications of vaccination so far as the skin is concerned in an endeavour to ascertain as accurately as possible the nature of the condition. (i) *Contact vaccination.*—This can be ruled out. Such transference could occur only in the susceptible phase, so that all the lesions (primary vaccination and those transferred) should progress more or less together and not more than a week apart. (ii) *Generalized vaccinia.*—No mention is made of an eczematous condition of the skin, so Kaposi's dermatosis may be excluded. Ordinary dissemination is possible as an explanation, but seems unlikely in view of the absence of constitutional upset. (iii) *Sensitization to calf lymph.*—Rashes—erythematous, papular, urticarial, and vesicular—may be encountered after vaccination and are akin to the "serum rashes" seen after the administration of antitoxins. These usually fade within seven to ten days of their appearance, but a longer duration is possible. Five weeks, however, does seem a rather excessive period. (iv) *Impetigo.*—It is assumed that a vesicular form of impetigo can be excluded.

It seems therefore most likely that a sensitization rash is the best explanation. The following observations are relevant. First, in the absence of an atopic eczema there is no reason to believe that subsequent vaccination would necessarily again be followed by dissemination of virus. Secondly, if sensitization is the cause one would expect further manifestations of sensitization to appear, and these should be looked for. If it was considered practicable a patch or scratch test with heated calf lymph (to destroy the virus) might be tried. Certainly it would be worth while carrying out this simple procedure before any subsequent vaccination.

Penicillin in Chronic Sinusitis

Q.—*Has any work been done on the treatment of chronic sinus infections by antibiotics, particularly those infections which cannot be treated by irrigation?*

A.—A great deal of work has been done on this problem, especially with penicillin. Boyd, in an article in the *Laryngoscope* (July, 1947), gives an excellent summary of the literature, and describes his own results in a small series of cases. He concludes that penicillin undoubtedly has a useful place in treatment. But here, as in all chronic infections of this type, the difficulty is to bring the antibiotic into contact with the organisms in adequate concentrations. For this reason the results of treatment are usually disappointing, even when the antibiotic is administered locally and parenterally over long periods.

NOTES AND COMMENTS

Cracked and Painful Fingertips.—Dr. H. MAITLAND MOIR (Midlothian) writes: Your pessimistic answer (July 15, p. 178) is surely unwarranted. "Circulatory, metabolic, or hormonal dysfunction, xeroderma, psoriasis, lichen simplex, constitutional background factors"—I have none of these, though I do have occasional "hacks," as we call them in Scotland. They are quickly curable and instantly relievable. I pass on Dr. Grant Peterkin's advice to me, which I have proved to be excellent. Dry the hack, open it up, and insert a piece of cobbler's wax about the size of a large pinhead. Hold the finger near the fire or radiator: the wax quickly softens, and is then pressed firmly into the hack. A small piece of adhesive tape may be used to cover up the black spot. A pennyworth of wax is enough to cure all the hacks in Europe.

Corrections

In a leading article entitled "Public Health Dispute" (August 5, p. 336), the Conditions of Employment and National Arbitration Order, 1940, of the Defence (General) Regulations, 1939, was incorrectly described as the National Arbitration Tribunal (Defence) Regulations, 1940.

We regret that Professor R. D. Passey's name was wrongly spelt in the article entitled "Diphyllobothrium Infestation and Anaemia in Great Britain" (July 22, p. 188), and also in the list of references (p. 192).

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